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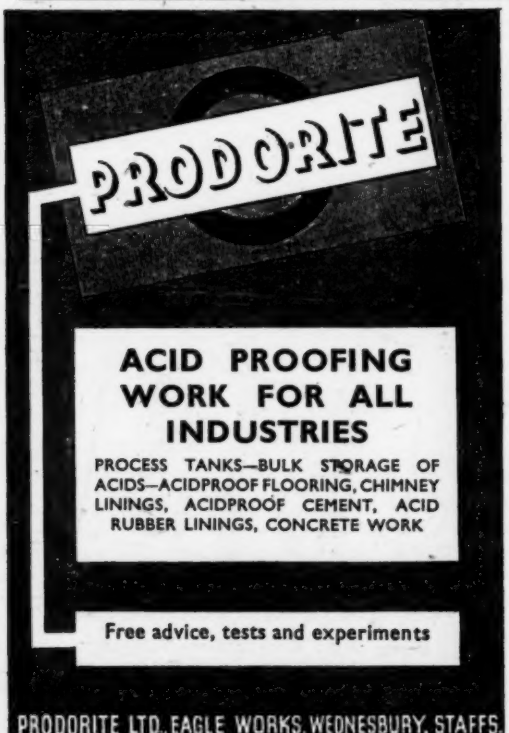
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LANCELOT SALISBURY BAGSTER.

1887—1940.

L. S. BAGSTER, D.Sc., Professor of Chemistry in the University of Queensland, Brisbane, died suddenly on March 14th, 1940, at the comparatively early age of 53.

Bagster was a graduate of the University of Adelaide, completing the course in science with first-class honours in 1908 under the late Professor Rennie. In the following year, he was appointed Government Research Scholar in the Department of Chemistry of the University of Melbourne and conducted research work under the general direction of Professor D. O. Masson.

When Professor Steele was appointed to the Chair of Chemistry in the University of Queensland, he urged strongly upon the Senate the desirability of giving special attention to chemistry in industry. In May, 1911, the Senate appointed Bagster and sent him abroad for approximately two years to gain the necessary industrial experience to enable him to take charge of this applied chemical work. He returned to these duties early in 1913, and from that date until his death was active in his University post.

He was a keen research investigator, and in 1920 gained the Doctorate of Science of the University of Adelaide, his main thesis being in connection with the effect of nitric acid on copper. In 1931, he was appointed in succession to Professor B. D. Steele to the Chair of Chemistry, and, as Professor of Chemistry, has, in addition to his onerous duties, had much to do with the designs of the new chemistry building to be erected at the University site at St. Lucia, Brisbane.

A foundation member of the Australian Chemical Institute, he always showed a lively enthusiasm for its welfare, and, in common with its founder, the late Sir David Masson, had strong views as to the services a chemist could render to the community. In this field of endeavour he gave his best.

Nine years ago he was President of the Queensland Branch of the Institute, and in association with the late Mr. G. J. Twine he assisted in the negotiations leading to the incorporation of the Institute by Royal Charter in 1932.

At the time of his death, Bagster was Dean of the Faculty of Science and had been a member of the Queensland State Committee of the Commonwealth Council for Scientific and Industrial Research for over 10 years. He was a Fellow of the Australian and New Zealand Association for the Advancement of Science and was President of the Chemistry Section at the Sydney meeting of that Association in 1932.

In personality, he was genial and unaffected, ever ready to help, and by reason of his general attitude of friendliness, his relationship with all those with whom he came into contact was invariably of the happiest nature.

T. G. H. JONES.

THOMAS BENNETT CASE.

1871—1941.

T. B. CASE was born on February 17th, 1871, and was educated at Winchester and Magdalen College, Oxford. He was a son of the President of Corpus Christi College, Oxford, and grandson of Sterndale Bennett, the composer. He took first class honours in Natural Science (Chemistry) at Oxford, and besides his scholastic attainments was a fine athlete, winning the Public Schools Doubles at rackets and obtaining his Blue at Oxford for cricket.

In 1893 Case joined the brewing staff of Guinness in Dublin at a time of considerable activity in the scientific world associated with the brewing industry. His influence was seen in the establishment in 1901 by the Directors of the Company, of the "Guinness Research Laboratory," in which he acted as Administrator, with Horace T. Brown as Research Director. To put the results of the "Guinness Research Laboratory" into practice, the firm erected an experimental brewery and an experimental malt house, and to carry out this work, Case enjoyed the collaboration of his colleague and brother-in-law (the late Alan McMullen). Methods developed under the research scheme were introduced into a routine laboratory which Case had inaugurated. Much information was thus acquired, and the data collected were examined statistically by another colleague, the late W. S. Gosset ("Student" of *Biometrika*).

Much of the original work of the laboratory was published in the form of "transactions," and the gist of it was given to the Institute of Brewing by H. T. Brown in 1907 in a paper entitled "The Nitrogen Question in Brewing."

After the initial work had been completed, the " Guinness Research Laboratory " was removed to other quarters, which it occupies to the present day. The character of the work changed somewhat to meet the special requirements of the Guinness products and their manufacture. Case, meanwhile, took up other activities in connection with brewing, never, however, losing touch with the work of the laboratories. When he became a Director of the firm in 1919, his interest in research was revived with renewed enthusiasm. With the passage of time the research laboratory has greatly increased in scope, particularly during the last 3 or 4 years. Yet Case, despite the increasing weight of responsibility due to world conditions, spared no pains to follow the latest developments, and was a constant source of inspiration to those who worked with him. His close touch with the laboratories, both routine and research, enabled him to put into practice in the main brewery such improvements as were indicated by the results obtained.

Thomas Case put his whole heart into everything he did. His friends will remember him chiefly for his extraordinary kindness, his courtesy, his self-effacement and his infinite capacity for taking pains in everything he undertook. They will be glad to know that his end was peaceful.

Case was elected a Fellow of the Chemical Society in 1895. He died on November 10th, 1941.

C. J. N.

WILLIAM LASH MILLER.

1866—1940.

WILLIAM LASH MILLER was born at Galt, Ontario, on September 10th, 1866. After graduation at the University of Toronto in 1887 he studied in Berlin, Göttingen, and Munich (Ph.D. 1890). He joined the staff at Toronto as fellow in 1890, was appointed lecturer in 1894, associate professor in 1900, and professor of physical chemistry in 1908. He became honorary member of the American Chemical Society in 1926 and Commander of the British Empire in 1935. During 1934—35 he was president of the Royal Society of Canada. He was retired at the age of 70 and became professor emeritus. He died on September 1st, 1940, after a two years' illness.

The death of William Lash Miller deprived the world of a great chemist and a great teacher. Miller dominated the chemical activities of Toronto for nearly fifty years. Although he was official head of the department of chemistry only since 1920, his dominant influence was felt from the time he joined the staff as fellow in chemistry in 1890; and yet " dominating " is the last word that could be used of his character. Insistent he was, and with good reason, for his decisions in the long run were always right, though they might at times be wrong for the moment in their effect on people. How often one heard " I disagreed with him at the time, I didn't like what he did, but he was absolutely right." All his work bore the mark of his extraordinarily accurate and logical mind and of his painstaking care. He had infinite patience with things, often little with people, but his small patience with human pettiness was more than made up for by his generosity of heart, innumerable instances of which have only come to light years later through casual mention by old students and friends.

He had little faith in formal lectures; during his own lecture hours he lounged on the edge of the table, smoking and talking cheerfully to his class, but the students neither lounged nor smoked, and woe betide any who missed one step in the relentless logic of his cheerful words. His terrifying insistence on clearness of thought and expression cut deep into his students and colleagues and left a lasting mark on their characters.

How great was Miller's contribution to science will probably not be fully realised until a new philosopher arises who does for chemistry what Ernst Mach did for physics; then Miller's fundamental thinking will be made plain to the ordinary man.

Miller's research work was so varied that it cannot be described in a few pages; it cannot even be found in the abstract indexes without careful search, for most of it he published generously under his students' names. Only the general outlines of his work will be indicated. His first physico-chemical research (1892) on the electromotive force of metal electrodes gave a confirmation of a prediction based on one of Willard Gibbs' equations. This was Miller's first introduction to Gibbs' thermodynamics, which became his predominant interest for a number of years and on which Miller's fame as a scientist and teacher chiefly rests. It was natural, therefore, that his first series of researches should be on equilibrium phenomena. Later, about 1902, he attacked the problem of reaction velocity and a long series of papers appeared on this subject. It was characteristic of him that during this work, being dissatisfied with the abstract journals of the time, he made a card catalogue of all rate measurements by paging over all the earlier volumes of the standard journals. Following this there were many publications on electrochemistry, transport numbers, overvoltage, diffusion and high-current arcs. In connection with his work on induced reactions and overvoltage he (with Roseburgh) published the first tables of certain

functions of e^{-x}, which have been widely used for other purposes since that time. In this period also appeared his well-known paper on "The mathematical treatment of diffusion and chemical action at electrodes" (with Roseburgh). A paper published much later (with Gordon) on "The numerical evaluation of series and integrals in problems of linear heat flow and electrochemical diffusion" may be included in this group.

In 1923 Miller was invited as one of the "seven most eminent physical chemists of the world" to give an address at the opening of the Sterling Laboratory at Yale. There resulted the publication of "The method of Willard Gibbs in chemical thermodynamics," in which a perfectly clear but comprehensive treatment of the subject is condensed into fifty pages, for Miller was one of the few who *could* write perfectly clearly about thermodynamics.

During the last twenty years of Miller's life bios claimed more and more of his interest; in all, about fifty-six papers were published on it and allied subjects. But the germ of the idea was already in his mind at a much earlier time. It was when he was writing his paper on the second differential coefficients of ζ in 1897 that the possible connection between the toxicity of phenol towards bacteria and its chemical potential occurred to him. The work on this idea led to the search for a less dangerous organism than anthrax or *staphylococcus* for the measurement of toxicity; and the study of yeast, chosen for this purpose, led to bios.

Of Miller's attitude towards scientific work, let his own words speak. After heartbreaking failures to get to the bottom of some problem which a lesser man would have given up as hopeless: "Never mind, the chemicals are trying to tell us something." His delight over a confirmation of some deductive reasoning, especially if the foundation for it was the potential concept of Willard Gibbs, is shown by his account (*Proc. Roy. Soc. Canada*, 1935) of the realisation of his prediction, from experiments with anthrax spores, "that mercuric chloride should be less soluble in 30% alcohol than in any other strength; we tried it, and by Jupiter it was—a curious way to predict solubility relations."

His method of investigation by deliberate concentration on a few ideas is also best given in his own words, in which, as always, he gives the credit to others: "They thought of microbes merely as a pinch of powdered chemical material, like some precipitate in a test-tube. . . . This was a narrow view to take. But the very division of Science into branches emphasises the importance of this narrow view, of concentration on a few ideas at a time. . . . Again, this chemists' point of view might seem too trivial to deserve attention. It is easy to imagine someone asking: 'you say a million microbes constitute a kind of dust, no doubt they do; what of it?' The proper answer to this question is 'Why then, mercuric cyanide will not be poisonous!' Links in the argument are here omitted, but they exist" (*Proc. Roy. Soc. Canada*, 1935). It was this apparently "trivial point of view" which was the foundation of all Miller's work on bios and which led him to success where specialists in bacteriology or zymology failed.

Miller was a conservative scientist "as all good scientific men should be," but he realised both the virtues and the defects of this attitude. After showing how many facts about the poisoning of micro-organisms could be explained on the theory of potential: "Perhaps you will excuse us for having got potential on the brain, as they say. It seems to me that it was not only excusable, but our bounden duty, and in the best scientific tradition. For, whether or no scientific discoveries are revolutionising the world, it is certainly true that the minds to which these discoveries are due are for the most part those of diehards; most of the millions of facts recorded in chemical handbooks are the results of pattern-work. Science is inherently conservative. . . . But when we tried acids as poisons instead of phenol, we suffered from the defects of our virtue, and went on poisoning yeast with acids for a whole year before realising that the toxic power of acids in moderately dilute solutions may have nothing whatever to do with potential, concentration, or p_H."

It is fitting to close this obituary with Miller's views on research work, as stated (*Proc. Roy. Soc. Canada*, 1935) in connection with *i*-inositol, which one of his students had identified as a constituent of bios: "Then, of course, there is Immortality. The hundredth part of one per cent. of Beilstein's handbook is given to *i*-inositol, two pages and a little overleaf out of the 22,479 to date. In the next edition or in a supplement, there will be added half a line: 'Active principle of Bios I, Eastcott, JPC **32** 1094.' This is immortality of a kind, for they print Beilstein on good paper; but it is the grey immortality of a breath of thought, immortality as conceived by Plato. Nothing in Beilstein of the winter spent on improving the analytical methods for phenol until they were adequate to potential determinations; nothing of the little group crowded round a kitchen table in the cellar while Clark plotted his rate measurements; nothing of the years of work before the first constituents of bios were obtained as crystals; nothing of the baffled instincts when the weaker phenol solutions proved more poisonous than the stronger, or when the potential concept failed us in the work on acids; nothing of the perplexities when one day the yeast would spore and the next day not. I sometimes wonder whether there is anything in Beilstein

half as important as the things he leaves out. From the University's point of view there certainly is not; for Universities exist to supply the world with trained men and women; supplying lines to Beilstein is a minor object. In fact the only justification for the years that students spend in cellars with professors, is the training they receive there; training not merely of the mind, but of the will and character as well. The ancient Persians were an outdoor folk, who, we are told, trained their children to ride straight, shoot straight, and tell the truth. Research chemists, unfortunately, must work indoors; but they can teach *their* children, children of the spirit, to work hard and like it, to think straight—and to tell the truth."

FRANK B. KENRICK.

LEONARD TEMPLE THORNE.

1855—1941.

IN 1873 Thorne became an assistant to Prof. Edward Frankland at the Royal College of Chemistry and after carrying out some work on the luminosity of benzene he was nominated by his Professor in 1875 to the first Jodrell Scholarship in Chemistry. He received the diploma of the College and then went to Würzburg and there took his first Ph.D. degree, an academic distinction rarely accorded at that time to English students. Towards the end of his studentship at Würzburg he became lecture assistant to Wislicenus and thus was probably the first Englishman to act as *Privat Docent* in a German University. On his return to this country Thorne became research assistant to W. H. Perkin. For a short time in 1886—7 he was a deputy for Prof. Humphridge at the University College, Aberystwyth. For the next 8 or 9 years he was chemist to Brins Oxygen Co., later known as the British Oxygen Co. In 1895 he became chemist to Garton Hill and Co., manufacturers of brewers' and confectioners' sugars, an appointment which he held until his retirement in 1935.

Early in life he associated himself with the activities of our Society and he found congenial work as Hon. Librarian, when, in 1884, he succeeded Henry Watts in that position. Those of us who were members in those days will not forget his kindly assistance in "reference hunting."

He was an original member of the Society of Chemical Industry and also took a very active interest in the Institute of Brewing, of which he was made an Honorary Member in 1939, a fitting acknowledgment of the work he had done for that body and of the regard in which he was held by the brewing industry.

Thorne was the "academic" type of chemist with an excellent knowledge of the literature of the subjects he was interested in. Although successful in his technical activities, those who knew him felt that he was more adapted to University than to factory life. The time he spent in Germany made a great impression on him and he had claims to be an authority on the writings of Goethe.

He was somewhat of a shy and retiring nature, but very kindly and gentle in his dealings with his fellow chemists, to whom he freely gave any assistance in his power. He was greatly respected and liked by those with whom he came in contact. He leaves a widow and two sons, one an engineer, the other Bishop of Nyasaland.

JULIAN L. BAKER.

X-Rays and the Stoicheiometry of the Proteins, with Special Reference to the Structure of the Keratin–Myosin Group.

A Lecture Delivered before the Chemical Society on November 20th, 1941.

By William Thomas Astbury.

The analysis of molecular structure implies two principal steps: discovering the nature and numbers of the various constituents, and discovering the plan on which they are put together. For the smaller molecules this is a question of relatively few atoms and radicals, but for the giant molecules that shoulder the burden of molecular biology we have hardly yet gone beyond the stage of thinking wistfully in terms of a multitude of sub-molecules—" residues " as they are commonly called, residues of sugars, amino-acids, nucleotides, and the like. Proteins are polypeptide chain systems, alone or in combination with accessory molecules or groupings. These systems are often heavily disguised, it is true, but it is still the considered verdict of most workers in the subject, as it has been since the beginning of the century, that they provide the best and most comprehensive interpretation yet devised. Put more precisely in the light of recent developments, proteins are built from *folded* polypeptide chains cross-linked through combinations and interactions between their side chains. The problem of protein structure, therefore, resolves itself in the first place into discovering the nature and numbers of the amino-acid residues present and their order in the chain or chains, and then above all—for a protein may readily lose its specific properties (become " denatured ") without suffering more than an almost negligible change in chemical constitution—determining the *configuration* of the chain or chains, and what it is that induces or maintains that configuration. The title of this lecture suggests that it relates to the numerical proportions of the amino-acid residues in proteins, and so it does, among other things; but it is not sound structure analysis, nor indeed is it possible, to consider the distribution and properties of these residues apart from the patterns they form; and so in the end we shall be talking about the whole architecture of proteins. To revert to our opening metaphor, the two principal steps in the molecular analysis of the proteins merge into one great steep climb.

In some ways we know more now about the general plan underlying protein architecture than about their exact chemical constitution. That they are most beautifully planned, and frequently perhaps down to the last atom, is undeniable when we contemplate the elaborate *X*-ray diffraction patterns of feather (Fig. 1) or porcupine quill (Figs. 5 and 6) for instance, or recall the facts of immunology and admire anew the ultra-centrifugal studies of Svedberg and his collaborators, or even when we sift the seemingly discordant chemical data, if we put aside unworthy doubts and do not look for the impossible. The major trouble at the moment, though, does rest with the chemical data, partly on account of inadequate or laborious technique, but also on account of analytical variations well outside the limits of experimental error. Certain protein analysts have maintained that the proportions of the amino-acids in proteins often approximate to simple fractions involving 2's and 3's, and Bergmann and Niemann [1] have put forward the hypothesis that the numbers of the various residues, and also the total number of residues in the molecule, are always expressible in the form 2^n3^m, but there are other biochemists who feel that the numerical agreements claimed are fortuitous, resulting from inaccurate analyses. Neither of these two extreme views can be wholly correct and neither wholly incorrect. For consider, *e.g.*, Bergmann's proposed analytical data for gelatin (Table I), from which, in conjunction with *X*-ray data, it has been found possible to deduce the general form of the intramolecular pattern along the polypeptide chains of the great collagen group of protein fibres.[2] Whether or not we accept the smaller estimated yields of

Table I.

Gelatin.

Estimated average residue weight = 94. No. of gram-residues in 100 g. of gelatin = 100/94 = 1·06.

Amino-acid.	Yield, %.	*M.*	G.-mol.	Frequency.
Glycine	25·5	75	0·34	$3\ (2^0 . 3^1)$
Proline	19·7	115	0·17	$6\ (2^1 . 3^1)$
Hydroxyproline	14·4	131	0·11	$9\ (2^0 . 3^2)$
Alanine	8·7	89	0·098	$9\ (2^0 . 3^2)$
Arginine	9·1	174	0·052	$18\ (2^1 . 3^2)$
Leucine–*iso*Leucine	7·1	131	0·054	$18\ (2^1 . 3^2)$
Lysine	5·9	146	0·040	$24\ (2^3 . 3^1)$

amino-acids—and it is obvious that high accuracy is necessary before we may affirm in these cases that the frequency is truly expressible in the form 2^n3^m—there is no such order of difficulty with the larger yields, and it is beyond doubt that almost exactly one-third of the residues in gelatin are glycine residues and nearly another third ($\frac{5}{16}$) are proline and hydroxyproline residues. Similar conclusions hold for

preponderating acids in other proteins: too many examples are known to satisfy convincingly the theory of sheer accident. To anyone with a grain of stoicheiometric faith it is abundantly clear that the proteins are at least trying to behave. The important point is to find out what they are aiming at, and not to devote meticulous pains just yet to the second or third decimal place, or to concentrate always on a few particular amino-acids. It is not as though the situation were new to us—it is not. In its way it is the old problem of the silicates, alloys, and mixed crystals all over again. *X*-Rays have shown that, however complicated the empirical formula for a silicate may be, and some colossal formulæ have been put forward in the past, it is the atom or radical *sites* that count. These always rest on a stoicheiometric basis, and the pattern they form in space is strict and relatively simple. Let us then approach the problem of protein structure from a similar point of view. Let us look for the stoicheiometric ideal, the intramolecular *pattern* on which the details are embroidered.

The problem is to reconcile irregularity of constitution with regularity of structure, and we postulate an intramolecular interchange, or potential interchange, not between individual amino-acid residues, but between certain *types* of residues.[3]

If there is anything at all in this idea, the fibrous proteins that constitute the keratin–myosin group present a striking example. There is no need to detail their properties again:[4] it will be sufficient to recall that this group includes all the mammalian hairs, horn, spines, etc., the fibrous proteins of the epidermis, and also the chief protein of muscle tissue, myosin; *i.e.*, practically all the fibrous proteins we know except those belonging to the collagen group.[2] Moreover, all the members of the group give similar *X*-ray diffraction patterns and have closely related long-range elastic properties. Their normal, unstretched form (α) is built from regularly folded polypeptide chains, whereas their stretched form (β) arises from the same chains pulled out almost straight. When the stretched fibres are let go in the presence of water or other polar molecules, they return spontaneously to the folded form: the basis of their long-range elasticity is an intramolecular, reversible transformation—the β-form, in fact, may be called a " mechanical stereoisomer " of the α-form with an elongation of roughly 100%.

It follows from the common features of their diffraction patterns (how very much alike they are will be evident from Figs. 2a and 2b) and their similar elastic properties that the fibrous molecules of the keratin–myosin group are all built to a common plan, the α-keratin configuration we may call it, that is remarkably persistent as regards its main outlines and dimensions—and this in spite of equally remarkable variations in chemical constitution, ranging from myosin at one extreme, through the epidermal proteins, to keratin at the other. For the purposes of this discussion I have collected together all the available analytical data for wool keratin in Table II, whereas Table III shows less complete data for rabbit myosin.

TABLE II.

Wool keratin.

I, Amino-acid. II, Molecular weight. III, Reported yields from 100 g. of wool. IV, Yield chosen as probably most nearly correct. V, Gram-residues in 100 g. of wool.

I.	II.	III.	IV.	V.
Glycine	75	0·58,[5] 6·5 [7]	6·5	0·0870
Alanine	89	4·13 [5]	4·13	0·0464
Valine	117	2·8,[5] 4·8 [8,m]	4·8	0·0410
Leucine, etc.	131	11·5,[5] 11·3 [8,b,m]	11·3	0·0863
Phenylalanine	165	4·0,[7] 3·75 [8,m]	3·75	0·0227
Proline	115	4·4,[5] 6·8 [8,m]	6·8	0·0591
Methionine	149	0·44—0·66,[9] 0·7 [8,m]	0·7	0·0047
Cystine/2	120	7·3,[5] 13·1,[6,7] 11·9 [12,e,f]	11·9	0·0989
Serine	105	0·1,[5] 10·3 [8,e,m]	10·3	0·0981
Threonine	119	6·4 [8,e,m]	6·4	0·0538
Tyrosine	181	2·9,[5] 4·8,[6] 4·5 [7]	4·65	0·0257
Aspartic acid	133	2·3,[5] 5·84,[12,e] 7·3 [10,e]	6·57	0·0494
Glutamic acid	147	12·9,[5] 15·3 [10,e]	14·1	0·0959
Arginine	174	10·2,[6] 8·7,[7] 10·4 [11]	10·3	0·0592
Lysine	146	2·8,[6] 2·5 [7]	2·65	0·0182
Histidine	155	6·9,[6,a] 0·7 [7]	0·7	0·0045
Tryptophan	204	1·8,[6] 0·7 [7]	1·8	0·0088
Total gram-residues from 100 g. of wool				0·8597 *
Amide nitrogen	14	1·2,[6] 1·37,[e,m,8] 1·37 [10,e] 1·14,[13,e,m,d] 1·12 [13,e,e]	1·13	0·081

Notes.—Numbers refer to literature references.

a, Without doubt excessive. *b*, Martin and Synge's work suggests a leucine : *iso*leucine ratio of about 4 : 1. *c*, Cotswold wool. *m*, Merino wool. *d*, 1·37 value corrected for decomposition of serine. *e*, Mild hydrolysis. *f*, Estimated as total –S–S– and –SH.

* Not, of course, significant to four figures. These have been retained throughout so as to average out in the addition.

FIG. 2*a*.

X-Ray sector comparison photograph of α-horn and α-myosin (M, *myosin*; H, *horn*).

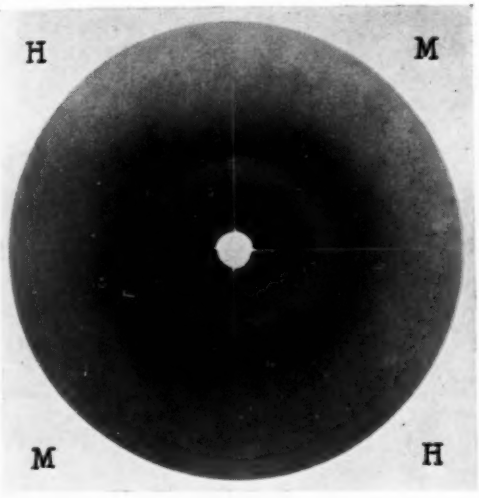
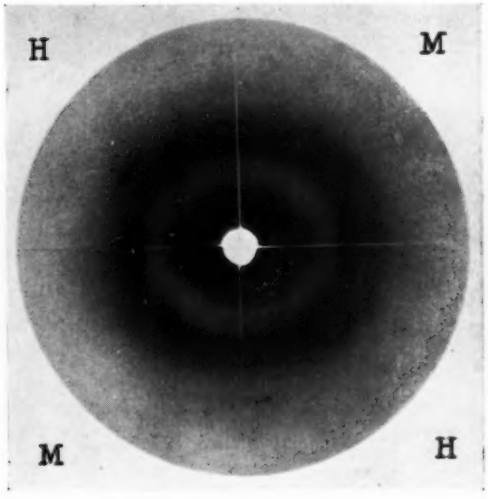


FIG. 2*b*.

X-Ray sector comparison photograph of β-horn and β-myosin (M, *myosin*; H, *horn*).



Cu-K_α *rays. Film-to-specimen distance* = 4 *cm.*

Each of these figures corresponds to two photographs taken on one and the same film, diagonally opposite quadrants being part of the same photograph. Each meridian or equatorial reflection is thus divided into two halves, one half arising from keratin and the other from myosin.

FIG. 1.

X-Ray "fibre photograph" of the quill of a sea gull's feather; Cu-K_α *rays; film-to-specimen distance, 5 cm.; X-ray beam parallel to the surface of the quill.*

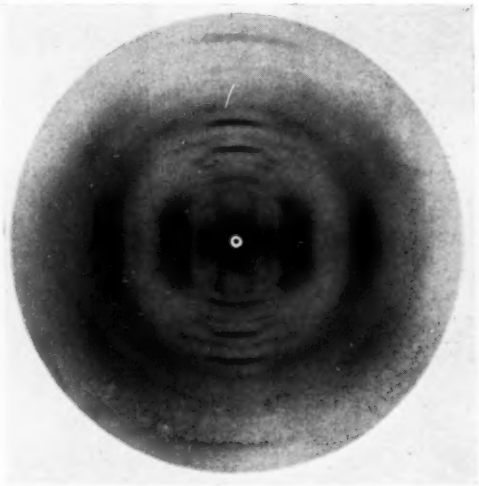
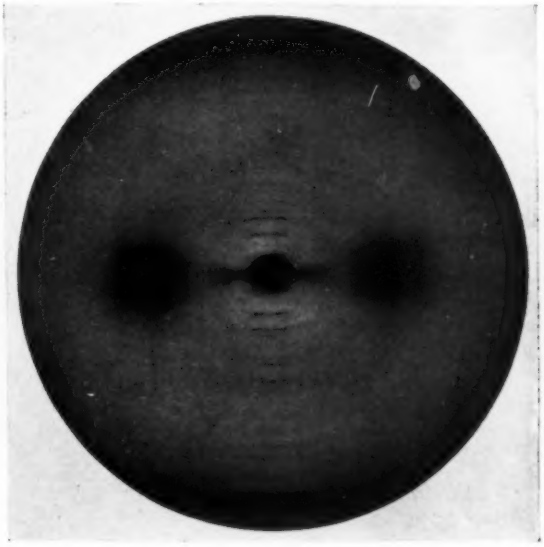


FIG. 3.

X-Ray fibre photograph of the tip end of a porcupine quill, dried in a vacuum over phosphoric oxide. Cu-K_α *rays. Specimen-to-film distance* = 9·7$_9$ *cm. Collimator* 13 × 0·025 *cm.* (*MacArthur.*)



[*To face p.* 338.

TABLE III.

Rabbit myosin.

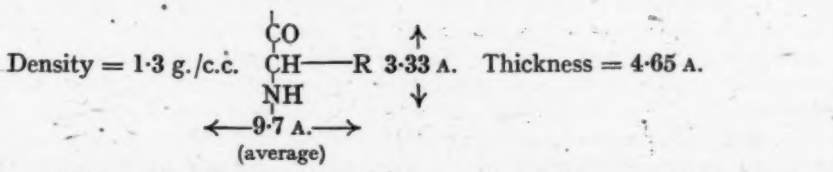
I, Amino-acid. II, Molecular weight. III, Most recently reported, and probably best, yields from 100 g. of myosin. IV, Gram-residues in 100 g. of myosin.

I.	II.	III.	IV.
Cystine/2	120	1·39 [18]	0·0116
(+ cysteine)	(121)		
Methionine	149	3·4 [14]	0·0228
Serine	105	3·57 [a]	0·0340
Threonine	119	3·81 [a]	0·0320
Tyrosine	181	3·4 [14]	0·0188
Aspartic acid	133	8·9 [16]	0·0669
Glutamic acid	147	22·1 [16]	0·1469
Arginine	174	7·0 [16]	0·0402
Lysine	146	10·3 [17]	0·0705
Histidine	155	1·7 [16]	0·0110
Tryptophan	204	0·82 [14]	0·0040
Glycine	75	1·9 [16]	0·0253
Alanine	89	5·1 [17]	0·0573
Valine	117		
Leucine, etc.	131	(*b*) —	0·2412
Phenylalanine	165		
Proline	115		
Total			0·7825
Amide nitrogen	14	$1{\cdot}19_3$,[17,a] $1{\cdot}19_5$ [15,a]	0·0852

Notes.—The yields quoted in the upper half of the table are more reliable than those quoted in the lower half. *a*, Mild hydrolysis. *b*, Sharp's yields of these four acids give together 0·1506 g.-residue, but Martin and Synge,[18] using their new chromatographic method,[19] have estimated for me that these four together with methionine account for probably some 22% of the total nitrogen. From Sharp's value of the total N (16·8%), and allowing for the methionine yield quoted above, this means that valine, leucine, phenylalanine, and proline give altogether 0·2412 g.-residue. Sharp recognises, however, that most of his shortage lies with the monoamino-acids, and the 9% missing even now may reasonably be ascribed chiefly to the glycine and alanine determinations.

At first sight it might appear rather hopeless, especially in view of the element of incompleteness and uncertainty, to try to co-ordinate these chemical findings with the *X*-ray data on keratin and myosin, but actually the latter give us at once the average amino-acid residue weight, and thence that important quantity that we must know from the outset, namely, the number of gram-residues in 100 g. of protein. The deduction follows from the average residue dimensions, as inferred from *X*-ray photographs of the fully-extended, or β-, form, and the density, thus:

β-*Keratin.*



Average residue mass $= 3{\cdot}33 \times 9{\cdot}7 \times 4{\cdot}65 \times 1{\cdot}3 \times 10^{-24}$ g. One-sixteenth of the mass of an oxygen atom $= 1{\cdot}65 \times 10^{-24}$ g. Therefore average residue weight $= \dfrac{3{\cdot}33 \times 9{\cdot}7 \times 4{\cdot}65 \times 1{\cdot}3}{1{\cdot}65} = 118$ (approx.) and number of gram-residues in 100 g. of keratin = 0·85.

Similarly, for

β-*Myosin*:

Average residue weight $= \dfrac{3{\cdot}3 \times 9{\cdot}8 \times 4{\cdot}65 \times 1{\cdot}275}{1{\cdot}65} = 116$ (approx.).

and number of gram-residues in 100 g. of myosin = 0·86.

From these calculations we see that the tale of amino-acid analyses for wool keratin is now on the average reasonably sound and complete: indeed, the grand total of the yields that I have chosen as most plausible amounts to somewhat more than the predicted. It seems best to assume that this error is fairly evenly distributed, and to base our subsequent calculations on the *X*-ray value. For myosin we see that the total yields still amount to only about 91% of the possible maximum, and so *a fortiori* we shall rely on the *X*-ray value. In any case, it must be understood quite definitely that the argument developed in this lecture does not rest at this stage, and is not intended to rest, on mathematically precise chemical analyses. We are trying to discover first the broad molecular plan underlying the keratin–myosin

group. In the end nothing will suffice chemically but complete analyses carried out each *on one and the same specimen of protein.**

The " broad plan " of the keratin–myosin group will have only an approximately constant weight, of course, but it should be founded on always the same number of amino-acid residues, and these should be susceptible of certain ideal distributions that, either singly, in combination, or after residue interchange, reproduce the various members of the group. For several reasons, none of them convincing, it must be granted, if taken alone, but impressive enough when weighed together, the number of residues typical of the group would appear to be either 576 or a multiple of 576. These reasons are as follows :

(1) Given an ideal plan—our fundamental postulate—it is not likely that this is going to be based on a series of mostly incommensurable numbers of residues, especially in molecules of such great size, which *X*-rays show in any case to be possessed of considerable internal regularity of pattern. The chemical analytical indications already noted, the *X*-ray evidence on porcupine quill to be adduced below, the recent stimulating findings of Pacsu [20] on the poly-condensation of certain peptide esters into chains of 3×2^n residues, the genesis of close-packed structures and more generally of the 32 crystallographic point-groups from aggregates involving factors of 2 and 3, all justify us in giving every chance, so to speak, to any attempt on the part of the data to conform to some such numerical system.

(2) The work of Svedberg and his collaborators, and related physicochemical investigations, point to the existence of groups of protein molecules of the same or closely similar architecture; and probably these groups are built in the first place from sub-groups containing at the most 144 ($2^4.3^2$) residues.

(3) Myosin incorporates as part of its more permanent make-up a small proportion of phosphorus. Bate Smith and Davis [21] have reported percentages ranging from 0·04 to 0·06, and Bailey's [12, 22] determinations include 0·043—0·050, 0·054, 0·055, 0·055, 0·048, and 0·067. The percentage corresponding to one atom of phosphorus per 576 residues of average weight 116 is 0·0463.

(4) Table IV, col. I, shows the " frequencies " † of the various amino-acid residues in wool keratin corresponding to the chosen experimental yields listed in Table II. They are remarkably close to the powers of 2 and 3 shown in col. II, which give residue numbers totalling exactly 576 (col. IV). (The residue numbers shown in col. III are derived from the experimental frequencies in col. I, and so add up to rather more than 576 because the total of the chosen experimental yields is a little too high—see above.) In a combination of, or an interchange between, ideal distributions of residues, we should not in general expect such close agreement between experimental and ideal frequencies; there is thus a further implication here, *viz.*, that the structure of the average wool approximates to an ideal distribution at the keratinous end of the keratin–myosin series.

Provisionally, then, we may suppose that the smallest " pattern weight " in wool keratin is about $576 \times 118 = 68{,}000$, and in rabbit myosin $576 \times 116 = 66{,}800$.

We are not yet in a position to draw up for myosin as complete a table as Table IV, but Table V shows the experimental numbers of residues for the more reliable amino-acids in myosin, side by side with corresponding keratin numbers abstracted from Table IV in order to facilitate comparison. In what follows, partly to disarm criticism on the score of making free with debatable Bergmann–Niemann numbers and partly because our argument makes it unnecessary to assume that either wool keratin or rabbit myosin conforms strictly to an ideal distribution, *we shall use only experimental values for both.* Tables IV and V illustrate at a glance the sort of stoicheiometric problem with which we are confronted. We have to correlate this wide range of chemical constitution with a common molecular pattern and similar long-range elastic properties. No simple correlation based on individual amino-acids seems at all possible: something broader is required. We have to apply the principle that the more things there are to be explained, the more fundamental must be the explanation. We must look for some structural property of supreme generality.

Let us turn now to the new α-model,[23] which certainly has this property of generality. It is based on the polypeptide " grid " and the close-packing of side chains, and it was derived from crystallographic, elasticity, and density considerations without reference to any particular side-chain distribution. A satisfactory atomic model has been constructed to scale,[23] but the diagrammatic representation in Fig. 3 will serve our purpose. The important point to notice is that the side chains are packed together in triads that occur first on one side of the main chain and then on the other.

In an attempt to give more purely chemical substance to this model, we first thought [23] that it meant

* It is almost useless to continue to estimate certain amino-acids on one kind of keratin and other acids on another kind; and if it is asked why I seem to have glossed over the question of the variable cystine content in keratin, I can only say that for want of data on *accompanying* variations in the other amino-acids I have done the next best thing, taken a cystine value representative of wool on the average—again, it must be repeated, with the object of trying to deduce the general scheme on which there are so many and so obvious variations.

† A frequency f for any amino-acid means that the residues of that acid amount to $1/f$th of the total residues in the molecule.

TABLE IV.

Wool keratin.

I, Experimental frequencies. II, Possible "ideal" frequencies corresponding to I. III, Experimentally determined approximate numbers of residues referred to a total of 576 ($2^6 . 3^2$). IV, Numbers of residues, totalling exactly 576, corresponding to the "ideal" frequencies given in II.

Amino-acid.	I.	II.	III.	IV.
Glycine	9·8	9	59	64
Alanine	18·3	18	31	32
Valine	20·7	24	28	24
Leucine, etc.	9·9	9	58	64
Phenylalanine	37·4	36	15	16
Proline	14·4	16	40	36
Methionine	181	192	3	3
Cystine/2	8·6	9	67	64
Serine	8·7	9	66	64
Threonine	15·8	16	36	36
Tyrosine	33·1	36	17	16
Tryptophan	96·3	96	6	6
Aspartic acid	17·2	16	34	36
Glutamic acid	8·9	9	65	64
Arginine	14·4	16	40	36
Lysine	46·7	48	12	12
Histidine	188	192	3	3
Totals			580	576
Amides	10·5	—	55	—

TABLE V.

Comparative chemical constitutions of wool keratin and rabbit myosin for the more reliable amino-acids.

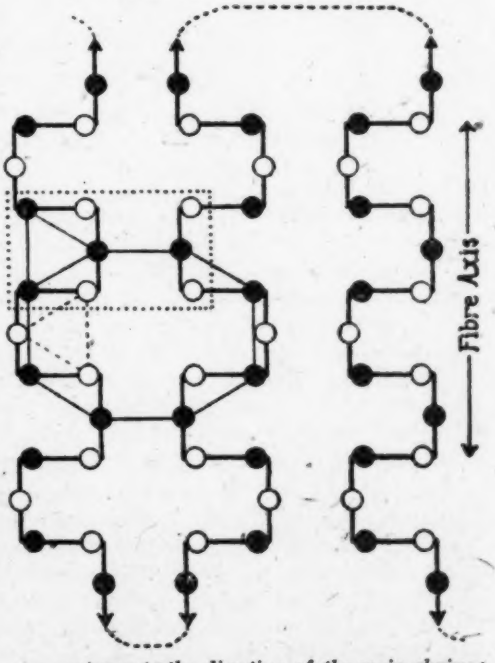
Amino-acid.	Observed approximate numbers of residues in 576. Wool keratin.	Rabbit myosin.
Cystine/2 + cysteine	67	8
Methionine	3	15
Serine	66	23
Threonine	36	21
Tyrosine	17	13
Tryptophan	6	3
Aspartic acid	34	45
Glutamic acid	65	98
Arginine	40	27
Lysine	12	47
Histidine	3	7
Amides	55	57

that the residues in both keratin and myosin fall into three equal groups, all the members of any one group being either chemically similar (like aspartic and glutamic acids) or probably related biogenetically, and therefore potentially interchangeable. From this point of view each triad of side chains would always include one member of each of the three groups. Further opportunity of examining the problem in the light of new chemical data [18, 24] does not favour this interpretation, however, but suggests rather that the paramount considerations are these: (*a*) The triads are formed from individual side chains that lie alternately on one side and the other of the main chain. (*b*) Martin and Synge [24] find that, in the dipeptides formed on incomplete hydrolysis of wool, the basic amino-acids, at least, are linked with all sorts of non-polar amino-acids—in fact, there seems to be no really outstanding difference between the distribution of acids in the dipeptides and that in the original polypeptide. (*c*) Polar side chains will tend to aggregate with polar side chains, and non-polar with non-polar.

Suppose now that the great common property linking keratin and myosin is simply this, that *individual side chains are alternately polar and non-polar*. We see then that, not only do we satisfy condition (*b*) and, because of (*a*), bring about (*c*) automatically, but also we endow the structure with potential long-range elasticity! First, though, let us make sure of the corollary that in spite of everything there are in both keratin and myosin approximately equal numbers of polar and non-polar side chains. Table VI shows that this is so—fortunately we can draw up such a table without undue worry about inadequate data on the non-polar side chains, since it happens that the estimates of all the polar side chains are sufficiently good. Theoretically, of course, we might expect 288 side chains of each kind in the total of 576, but we have no right to insist on exact agreement, partly because of analytical errors that have doubtless not yet been eliminated from Table VI, but chiefly because what we have just postulated about the sequence of side chains, though fundamental, may not be the whole story: it may be that the

FIG. 3.

Illustrating the packing of side chains in the α-fold of the keratin–myosin group.



— represents the direction of the main chains; ● represents a side chain pointing up *from the plane of the diagram; ○ represents a side chain pointing* down *from the plane of the diagram.*

TABLE VI.

Summation of polar side chains in keratin and myosin (experimental values).

Acid.	Gram-residues. Keratin.	Gram-residues. Myosin.	Nos. of residues. Keratin.	Nos. of residues. Myosin.
Arginine	0·0592	0·0402	40	27
Lysine	0·0182	0·0705	12	47
Histidine	0·0045	0·0110	3	7
Aspartic acid	0·0494	0·0669	34	45
Glutamic acid	0·0959	0·1469	65	98
Serine	0·0981	0·034	66	23
Threonine	0·0538	0·032	36	21
Tyrosine	0·0257	0·0188	17	13
Totals	0·4048	0·4203	273	281
	out of 0·85	out of 0·86	out of 576	out of 576

Note.—In myosin there are also on the average about 2 cysteine residues.[25]

plan is adhered to in general, but certain divergences are permissible in detail, or are essential to serve ends we do not yet appreciate.

As for the explanation the theory offers of the long-range elasticity of the keratin–myosin group, it is easy to raise points of detail to which there are no immediate answers, but nevertheless the new outlook appears more promising in scope than anything that has gone before. It must be repeated that we have to explain similar long-range elastic properties and the same α–β transformation in the face of startling variations in chemical constitution,* and we are suggesting quite broadly that the phenomenon is to be traced throughout the group to a common mode of side-chain aggregation involving the formation of polar triads on one side of the folded main chain and non-polar triads on the other. There is nothing here, be it noted on the one hand, to say that *all* one side of a folded main-chain shall be polar and all the other side non-polar—rather might we expect alternations of polar and non-polar surfaces at intervals decided perhaps by the intervention of proline residues—and there is no question of dispensing with the initial driving force of contraction associated with the stressed side-chain linkages of the β-form,[26] or of minimising the hydrogen bridges between CO– and NH– groups that appear in the atomic model both within and between the α-folds.[23] On the other hand, there is room for an eventual interpretation of the contraction of muscle in terms of increased facilities for aggregation induced by comparatively simple reversible changes in the relative distributions of polar and non-polar side chains, and above all, there is a prospective harmonising of the concepts that myosin is both the working elastic mechanism in muscle and also a principal enzyme (adenosine triphosphatase [27]) in the elastic cycle. By the incorporation of specific reactive groupings among the polar side chains, the characteristic elastic features of the group would rest unimpaired, but the versatility or sensitivity of the system might very well be increased in relation to a particular chemical environment.

We continue with the constitution of the individual polar triads, on which depend in the main the power of aggregation and the strength of inter-chain linkage. Tables IV and V, at the lowest stoicheiometric assessment, discourage any idea of arbitrariness, but quite apart from that there must be some rational scheme of combination or interaction between the polar side chains of neighbouring main chains in the polypeptide grid. Let us consider, then, of what kinds these cross-linkages may be, granted that we have at our disposal only side chains whose end groups are acidic, basic, hydroxyl or amides. Besides salt-like linkages between the bare acidic and the basic side chains, obviously there can be a variety of polar attractions (or hydrogen bridges), and principally the latter will lie between amide and hydroxyl end groups and between hydroxyl and hydroxyl end groups.† Table VII shows the comparative distribution of the different side chain end groups in wool keratin and rabbit myosin, together with a proposed scheme of cross-linkage between opposed polar triads of the polypeptide grid. Fig. 4 illustrates this scheme diagrammatically within the framework of the α-fold as depicted in Fig. 3.

We are converging now, it will be seen, on our original analogy between the stoicheiochemistry of the proteins and that of mixed crystals, such, for example, as the plagioclase felspars, built from continuously varying proportions of albite ($NaAlSi_3O_8$) and anorthite ($CaAl_2Si_2O_8$). Further, just as in these felspars

* It was surprising, too, how many liberties could be taken with the side chains of wool, *e.g.*, deamination of the basic side chains, without seriously upsetting the α–β transformation and the principal elastic properties. All that is now, at least, not surprising. Deamination is in effect no more than the replacement of one polar side chain by another.

† It may be recalled that the strength of the cellulose fibre rests largely on interactions between the hydroxyl groups of neighbouring β-glucose residues.

TABLE VII.

Comparative distribution of polar side chains in keratin and myosin.

	Keratin.		Myosin.	
	Analysis.	Titration.	Analysis.	Titration.
Basic	55	51—55 [28,a].	81	90,[29] 98,[30] 100 [31]
Acidic	44	—	86	87 [31]
Amide	55	—	57	—
Hydroxyl	119	—	57	—

Suggested approximate scheme of cross-linkage between opposed triads in keratin:

1. Acid–base.
2. Amide–hydroxyl (with some replacement by acid–base).
3. Hydroxyl–hydroxyl (with some deficiency probably made up by cystine linkages).

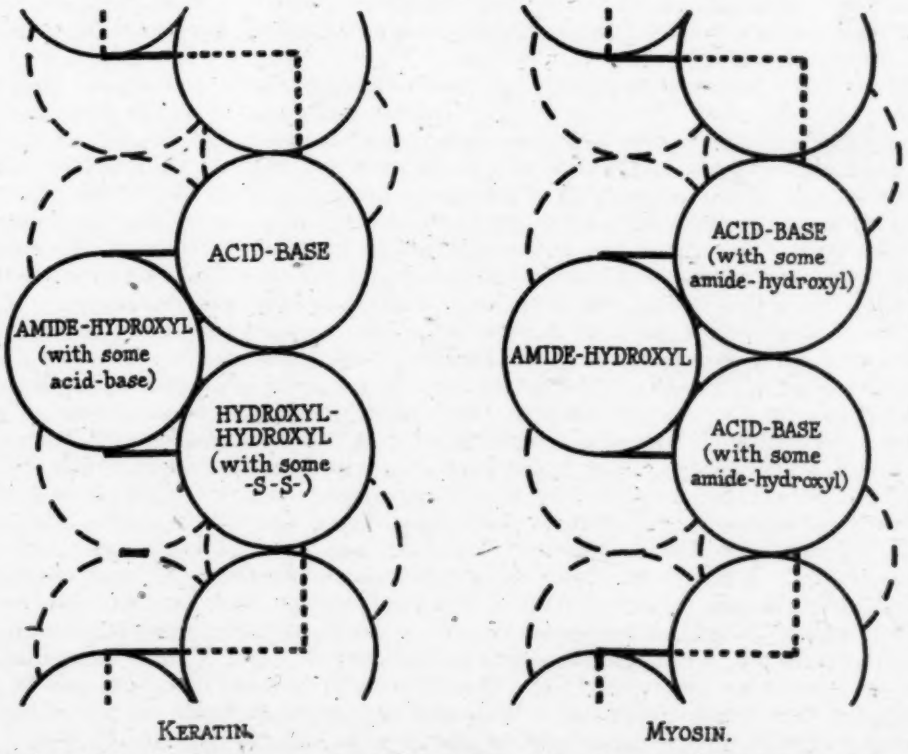
Suggested approximate scheme of cross-linkage between opposed triads in myosin:

1. Acid–base (with some replacement by amide–hydroxyl).
2. Amide–hydroxyl.
3. Acid–base (with some replacement by amide–hydroxyl).

Note (*a*).—A variety of wools and human hair. The best titration value for Cotswold wool [32] is probably 79·6 c.c. of N-HCl per 100 g. of wool, corresponding to approximately 54 basic side chains.

FIG. 4.

Proposed plan for the packing and cross-linkage of the polar side chains in keratin and myosin.



KERATIN. MYOSIN.

we have these two " ideal " structures at each end of the series, so in effect Table VII and Fig. 4 postulate an ideal limiting keratin and an ideal limiting myosin. Of the polar cross-linkages in the limiting keratin, one-third are salt linkages, one-third amide–hydroxyl bridges, and one-third hydroxyl–hydroxyl bridges; whereas in the limiting myosin two-thirds are salt linkages and one-third amide–hydroxyl bridges. Rabbit myosin itself is not far removed from the limiting myosin, which would require 96 acids, 96 bases, 48 amides, and 48 hydroxyls; but the situation with regard to wool keratin is hardly so simple just yet, possibly because the available analyses do not refer all to one and the same specimen of wool. There is a striking apparent deficiency of acids, even with the recent much improved yields, but whether this represents a true unbalance or whether, as suggested by titration * and the evidence for salt linkages advanced by Speakman,[33] it is an erroneous finding, is difficult to decide without more comprehensive experimental data. In this connection, however, it is noteworthy, as pointed out by Speakman,[33] that the proportions of the basic amino-acids vary little in the wools, so it is much less likely that the error—

* The titration curves of keratin and myosin are of a similar type.[29]

if there really is an error—lies with the bases than with the acids. It may be noted also that biochemists seem to be agreed that the amide nitrogen determinations are now fairly sound.

The position of cystine has long excited interest, so much so, in fact, that it has tended to blind protein chemists to the importance of the sixteen or so other amino-acids in wool. It is well known that keratin yields relatively enormous and highly variable quantities of cystine, as opposed to the small and almost constant proportion in myosin, but such knowledge is all but valueless until we know what happens simultaneously to all the other acids. Until we know that, the protein conscience is troubled and confidence is undermined. In the keratin–myosin group there are two ways of looking at the cystine content.[34] The first is to suppose it to consist of two parts, a small and constant proportion of "constitutional" cystine as in myosin, together with a large and variable proportion of "supplementary" cystine incorporated during the process of "keratinisation" to form a kind of cementing substance surrounding chain-bundles whose inner structure remains more or less unchanged. This view has been considered elsewhere,[34] but here we adopt the second, in which the cystine is judged to be always "constitutional," taking its place with the other acids in a molecular plan peculiarly adapted to their mutual interchange. The second hypothesis appears the more satisfying now that fuller chemical analyses are available, for the first does not accord at all well with the revolutionary changes, as we pass from myosin to keratin, in the *relative* proportions of the acids other than cystine, or with the fact that wools of different sulphur content show a roughly constant acid-combining power. It might be argued, of course, that "supplementary" cystine is combined with other acids in the supposed inter-myosin cementing substance; but such a contention begins to encroach on the second hypothesis and might well bring us back again only to the formation of another keratin.

Table VII and Fig. 4 make it clear why myosin is so much more reactive and so much more susceptible to inter-chain ("intra-micellar") swelling by polar reagents than keratin is. In myosin there are few or no vacancies for disulphide bridges among the polar cross-linkages, but in keratin we are obliged to use some of the cystine to make up the deficiency in the hydroxyl bridges. On this view the rest of the cystine in keratin, and all or practically all of the cystine in myosin, is distributed among the non-polar triads on the other face of the α-fold, where, as a sulphur acid, it is presumably just as acceptable as among the polar triads. It may or may not be of significance that the $-CH_2-S-S-CH_2-$ bridges on the polar face are to be found among the hydroxyl cross-linkages, but it is certainly suggestive that the serine side chain, $-CH_2-OH$, is the one that stands in closest chemical relation to these bridges.

It would not be justifiable at this stage to try to wring from our model any more chemistry, stoicheiometric or otherwise. The interpretation of the keratin–myosin group that we have just examined co-ordinates more facts and is far more promising than anything advanced before, but its chief function at the moment must be to draw ever more attention to the splendid opportunities offered by the group. Above all we need exact chemical analyses, and especially of the keratin of porcupine quill, which gives such excellent *X*-ray fibre photographs. Our earlier photographs of porcupine quill, though they indicated beyond doubt the presence of higher spacings, were like those of horn, for example, shown in Fig. 2; but now MacArthur,[35] working with greatly improved technique, has brought to light more than 100 reflections, ranging in spacing from 1 A. to 100 A., that together build up one of the most perfect protein fibre patterns yet encountered. Fig. 5 is a reproduction of the central region of the porcupine quill photograph. The prominent group of reflections near the top and bottom corresponds to the arcs—the only arcs—seen in Fig. 2, so it will be appreciated how very much more crystallographic information is now at our disposal. To emphasise this point, Fig. 6 is a composite diagram that includes most of the α-keratin pattern as we know it now—it is inspiring, to say the least. Given adequate chemical data, it should be possible to work out this pattern in considerable detail. With such data as are available the task of interpretation is already being proceeded with, of course, and an interim report may be expected shortly.

The perfection of the porcupine quill diffraction diagram is an expression of regularity of structure: this type of keratin, at any rate, is no haphazard affair. The molecular pattern is obviously approaching an "ideal," and surely there will be found a corresponding perfection of stoicheiometry among the constituent amino-acids. May it not be that the keratin of porcupine quill is actually the limiting keratin envisaged in Fig. 4, or something near it? We know little yet of the chemistry of porcupine quill, but there is one experimental fact known that lends colour to this suggestion, and that is that the sulphur content is quite low as compared with that of wool.*

The molecular pattern along the fibre axis of porcupine quill repeats at probably 658 A. (this is a minimum distance to date), and the strong meridian reflection of spacing 5·14 A. that is so characteristic of the keratin–myosin group is the 128th (2^7th) order of that period. If 5·14 A. represents the length of

* Rimington [36] found 1·35% of sulphur for the whole quill, 1·50% for the cortex, and 1·24% for the medulla. These analyses refer to complete quills, whereas the most perfect *X*-ray photographs are given by the tips, the rest of the cortex giving photographs approximating more to those of wool and hair. Possibly, then, the tips will be found to be still more deficient in sulphur.

an intramolecular fold comprising three residues, as we believe, then a single chain of the pattern-length revealed by *X*-rays would contain 384 ($2^7.3$) residues, or a multiple thereof. Chemical analysis indicates 576 ($2^6.3^2$), it will be recalled, but there is no real conflict, not only because both the *X*-ray and the chemical analytical numbers quoted must be considered for the present as the smallest compatible with the experimental data, but also because the chain may well be folded into long loops—it is easy, in fact, to suggest a type of loop that would conform with both numbers. The important thing to notice is that 384 is of the form 2^n3^m; and moreover that *almost all the dominant reflections along the fibre axis of porcupine quill are orders of* 658 A. *that are exactly or nearly of the form* 2^n3^m. These reflections are tabulated in Table VIII, due to MacArthur. In the left half of the table we see that *all* meridian reflections of appreciable strength included between the centre of the photograph and the reflection at 5·14 A. follow the rule closely, while in the right half there are still seven other dominant reflections, of smaller spacing, that show a similar tendency.* It cannot be argued that all this is pure coincidence, for in the crystallographic spacings listed there is none of the wide margin of experimental error overlapping hoped-for results that has been used as an argument against similar chemical agreements.

Here then, from a new and independent quarter, are our 2's and 3's all over again. It is impossible to dismiss them lightly as an example of wishful thinking. What they signify in the case of α-keratin is this, that the full molecular pattern is made up of smaller pseudo-patterns, just as that of the tobacco mosaic virus is,[37] and these pseudo-patterns subdivide the main pattern, sometimes more sharply, sometimes less sharply, into fractions of the form $1/2^n3^m$. It is to be noted that this is not the same thing as the Bergmann–Niemann theory [1] of the way in which the amino-acid residues follow one another along the polypeptide

FIG. 6.

Composite diagram of the α-keratin diffraction pattern given by porcupine quill (Cu-K_α *rays). The spacing of the most prominent arc on the meridian is* 5·14$_7$ A. (*MacArthur.*)

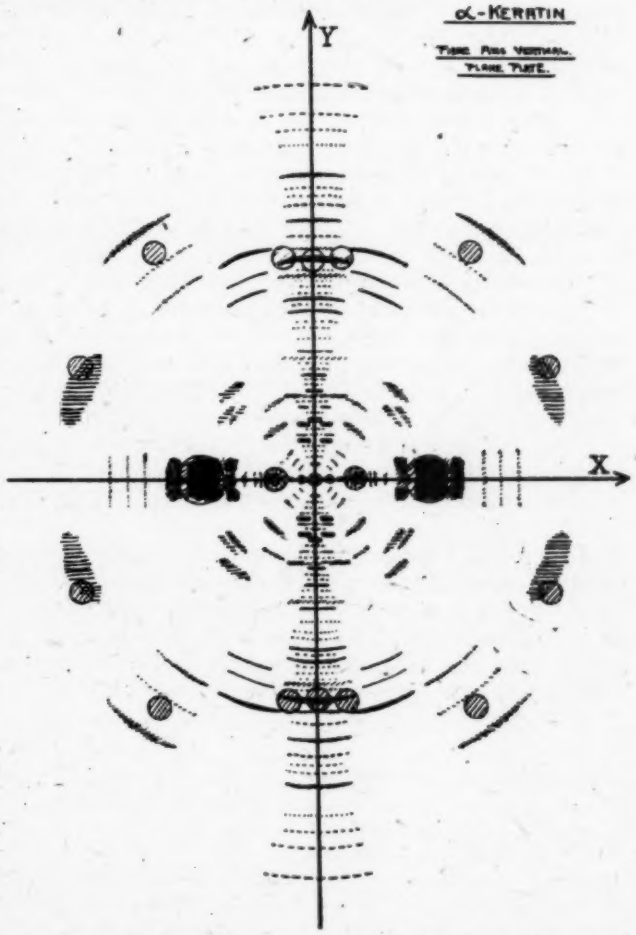


TABLE VIII.

Distribution of the main reflections along the fibre axis in the X-ray diffraction pattern of porcupine quill (α-*keratin*).

All meridian, or very near meridian, reflections ($d \geq$ 5·1 A.) with intensity $\geq$ W +:				Other dominant meridian reflections:			
Intensity.	Spacing, A.	Order of 658 A.	Nearest 2^n3^m.	Intensity.	Spacing, A.	Order of 658 A.	Nearest 2^n3^m.
M	66·3	10	9	M	4·45	148	144
M	27·8 *	24	24	W−	4·00	164	162
M	19·9$_5$ *	33	32	W−	3·41$_5$	193	192
WM	18·10	36	36	W+	3·08	214	216
W+	13·11	50	48	v.W	2·55	258	256
M−	12·35	53	54	(?)	2·29	287	288
W+	10·44	63	64	M+	1·49	442	432
M−	6·16	107	108				
Strong	5·14	128	128				

* Layer line spacing.

Intensities: M = moderately strong; W = weak; v.W = very weak.

* We should expect, in any case, the influence of the relative proportions of the residues to die out in reflections of smaller spacing, because the intensities of the latter will be decided more by the arrangement of atoms *within* the residues.

chain; and further, that it raises the status of col. IV, Table IV, to something higher than might be perceived through the gloom of stoicheio-pessimism.

Our last point in this lecture concerns the interpretation to be put upon the large side-spacings (up to 81 A., at least, and possibly including one of 109 A.) found in the *X*-ray diffraction pattern of porcupine quill. Large side spacings are found also in the diffraction diagrams of collagen, feather keratin, and other fibrous proteins, and beyond doubt they are of the very essence of the stoicheiometric problem. Unfortunately, they are mostly harder to resolve in the photographs than the meridian spacings are, and we have no really satisfying idea yet of their precise geometrical relationships. They show that the complete structural unit is built from a number of different, or differently oriented, polypeptide chains lying side by side. It follows from this that we are not restricted to the use of a single chain in our scheme of residue interchange; a similar end can be achieved by using varying proportions of certain types of chain, or of certain types of grid. Each of these types might be characterised by a constant stoicheiometric make-up, perhaps relatively simple, and perhaps based unequivocally on powers of 2 and 3. This approach again reminds us of some of the felspars and their recent *X*-ray interpretation in terms of a system of fine lamellæ.[38] There is much to be said for it, but the time is not yet ripe for a full discussion. I wish merely to stress again the crystallographic analogy, and to show once more how, by combining in this way the *X*-ray and the chemical viewpoint, we may come in time to see our problem in its true light.

That is the prime object of this lecture. I do not mean that I have not weighed the evidence carefully before making any suggestion—on the contrary—but I do mean that so many things are far from clear, and that the present interpretation is no more than a working hypothesis, an attempt to see just how we stand and just how we should proceed in this greatest of stoicheiometric quests. There is a touch of propaganda in this lecture, too, intentional propaganda; but it is of the benevolent kind, directed towards a closer and more understanding co-operation between the physics and chemistry of proteins. This is not the time, I know, in the midst of this war, to call on people for full-time, disinterested research, but it is good to keep the torch of knowledge alight, if only dimly.

I should like to acknowledge my indebtedness and express my thanks to Dr. Florence O. Bell for her unfailing personal help in this and similar investigations, to Dr. I. MacArthur for the use I have made of his invaluable *X*-ray results on the structure of porcupine quill, and to Mr. W. R. Atkin and Drs. K. Bailey, A. J. P. Martin, and R. L. M. Synge for helping me to collect my chemical data and for putting their own results at my disposal. Further, I should like to absolve all chemists of responsibility should it appear to some that I have misused the chemical data.

References.

[1] *J. Biol. Chem.*, 1936, **115**, 77; 1937, **118**, 301; *Science*, 1937, **86**, 187.
[2] Astbury, *J. Intern. Soc. Leather Trades' Chem.*, 1940, **24**, 69 (First Procter Memorial Lecture); Astbury and Bell, *Nature*, 1940, **145**, 421.
[3] Astbury, *ibid.*, 1937, **140**, 968.
[4] See, *e.g.*, Astbury and Dickinson, *Proc. Roy. Soc.*, 1940, *B*, **129**, 307.
[5] Abderhalden and Voitinovici, *Z. physiol. Chem.*, 1907, **52**, 348.
[6] Marston, Council of Scientific and Industrial Research, Commonwealth of Australia, 1928, Bulletin 38.
[7] Block, *J. Biol. Chem.*, 1939, **128**, 181.
[8] Martin and Synge, *Biochem. J.*, 1941, **35**, 294.
[9] Barritt, *ibid.*, 1934, **28**, 1.
[10] Speakman and Townend, *Nature*, 1937, **139**, 411.
[11] Vickery, *J. Biol. Chem.*, 1940, **132**, 325.
[12] Bailey, private communication.
[13] Gordon, Martin, and Synge, *Biochem. J.* (in the press).
[14] Bailey, *Biochem. J.*, 1937, **31**, 1406.
[15] *Idem*, *ibid.*
[16] Sharp, *ibid.*, 1939, **33**, 679.
[17] *Idem*, private communication.
[18] Private communication.
[19] *Biochem. J.* (in the press).
[20] *Nature*, 1939, **144**, 551; *J. Franklin Inst.*, 1940, **230**, 132.
[21] Rep. Food Investigation Board, D.S.I.R., p. 22.
[22] *Biochem. J.*, 1942, in the press.
[23] Astbury, *Chem. and Ind.*, 1941, **60**, 41, 491 (Jubilee Memorial Lecture); Astbury and Bell, *Nature*, 1941, **147**, 696.
[24] Gordon, Martin, and Synge, *Biochem. J.* (in the press).
[25] Mirsky, *J. Gen. Physiol.*, 1936, **19**, 559; Todrick and Walker, *Biochem. J.*, 1937, **31**, 292; Greenstein and Edsall, *J. Biol. Chem.*, 1940, **133**, 397.
[26] See, *e.g.*, Astbury and Woods, *Phil. Trans.*, 1933, *A*, **232**, 333.

[27] Engelhardt and Ljubimowa, *Nature*, 1939, **144**, 668; Ljubimowa and Engelhardt, *Biochemia*, 1939, **4**, 716; Engelhardt, Ljubimowa, and Meitina, *Compt. rend. Acad. Sci. U.R.S.S.*, 1941, **30**, 644; Needham, *Biochem. J.*, in the press; Bailey, *Biochem. J.*, in the press.
[28] See references in various papers by Speakman and collaborators, and by Harris.
[29] Atkin, private communication.
[30] Bailey, private communication.
[31] Salter, *Proc. Soc. Exp. Biol. Med.*, 1926, **24**, 116.
[32] Speakman and Stott, *Trans. Faraday Soc.*, 1935, **31**, 1425.
[33] *J. Text. Inst.*, 1941, **32**, 3 (Mather Lecture).
[34] Astbury and Dickinson, *Proc. Roy. Soc.*, 1940, *B*, **129**, 968.
[35] *Wool Rev.*, Jan. 1940, p. 9; Reports of the International Wool Secretariat; and in the press.
[36] In Bekker and King, *Biochem. J.*, 1931, **25**, 1077.
[37] Bernal and Fankuchen, *J. Gen. Physiol.*, 1941, **25**, 111.
[38] Chao and Taylor, *Proc. Roy. Soc.*, 1940, *A*, **176**, 76.

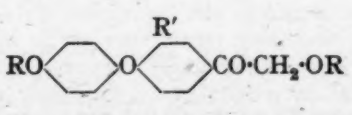
57. *Experiments on the Synthesis of Potential Cortical Hormone Substitutes. Hydroxy-carbonyl Derivatives of Diphenyl Ether and Related Compounds.*

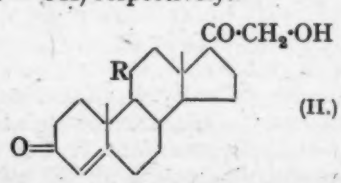
By James Walker.

Proceeding from the observation that 4 : 4′-dihydroxydiphenyl ether appeared to cause an increase in the liver glycogen of the fasting rat, a number of derivatives of diphenyl ether have been synthesised for examination for cortical hormone activity; these included *ω-hydroxy-4-(4′-hydroxyphenoxy)acetophenone* and its *diacetate*, *ω : 3-diacetoxy-4-(4′-acetoxyphenoxy)acetophenone*, *4-(4′-hydroxyphenoxy)-acetophenone* and *3-hydroxy-4-(4′-hydroxyphenoxy)acetophenone*. The second, fourth, and fifth of these substances gave no response when tested for progesterone activity. Tests for cortical hormone activity are not yet complete.

The extension in our knowledge of the adrenal cortex in recent years through the isolation therefrom of numerous closely related steroid hormones has stimulated interest in the therapeutic applications of these substances. Their very restricted availability, however, urgently prompts one to inquire into the possibility of elaborating substances in the laboratory, which would bear the same relationship to the cortical hormones as that of stilbœstrol and hexœstrol to the female sex hormones. The functions of the cortical hormones, however, are manifold and not coterminous, so that, while certain members of the group are predominantly of importance in carbohydrate metabolism, others are concerned in the maintenance of salt-water equilibria (compare, for example, Thorn, Engel, and Lewis, *Science*, 1941, **94**, 349). Consequently, the examination of any substance for cortical hormone activity is, of necessity, relatively complex, and the criteria which any synthetic compound must fulfil are more exacting in comparison with synthetic œstrogens, where biological differences, among compounds showing activity at all, are essentially in degree rather than in kind.

A possible clue to the type of compound which might be active was provided in this Institute by the observation that 4 : 4′-dihydroxydiphenyl ether, administered subcutaneously in nut oil, appeared to cause an increase in the liver glycogen of the fasting rat (Marks and Young, unpublished). This effect was observed in two experiments and with two specimens of dihydroxydiphenyl ether of different origins, although later experiments have failed to elicit the phenomenon, and the activity of this compound must therefore be regarded as still *sub judice*. The view was taken, however, that the diphenyl ether nucleus should be adopted as a basal unit to carry hydroxyl groups and the α-ketol side chain, characteristic of certain of the cortical hormones, as functional groups. With that object in mind, the syntheses of ω-hydroxy-4-(4′-hydroxyphenoxy)acetophenone (I; R = R′ = H) and ω : 3-dihydroxy-4-(4′-hydroxyphenoxy)acetophenone (I; R = H, R′ = OH) were undertaken as possible analogues of deoxycorticosterone (II; R = H) and corticosterone (II; R = OH) respectively.

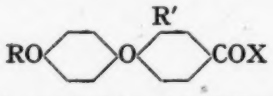
(I.) 

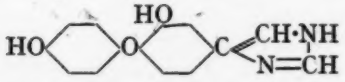


(II.)

The Ullmann condensation between *p*-bromoanisole and ethyl *p*-hydroxybenzoate in the presence of copper bronze and anhydrous potassium carbonate afforded a good yield of 4-(4′-methoxyphenoxy)-benzoic acid (III; R = Me, R′ = H, X = OH) (cf. Harington, *Biochem. J.*, 1926, **20**, 300; Harington

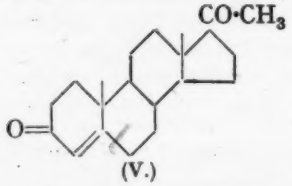
and Pitt-Rivers, J., 1940, 1101). Demethylation with hydrobromic acid in aqueous acetic acid proceeded smoothly to yield 4-(4′-*hydroxyphenoxy*)*benzoic acid* (III; R = R′ = H, X = OH), and the *ethyl* ester (III; R = R′ = H, X = OEt) was prepared by the Fischer–Speier process. Protection of the hydroxyl group in the hydroxy-acid was smoothly accomplished by using Chattaway's technique (J., 1931, 2495) and subsequent treatment of the *acetoxy-acid* (III; R = Ac, R′ = H, X = OH) with thionyl chloride and then with diazomethane afforded ω-*diazo*-4-(4′-*acetoxyphenoxy*)*acetophenone* (III; R = Ac, R′ = H, X = CHN_2). Treatment with glacial acetic acid then yielded ω-*acetoxy*-4-(4′-*acetoxyphenoxy*)*acetophenone* (I; R = Ac, R′ = H), from which, on hydrolysis, ω-*hydroxy*-4-(4′-*hydroxyphenoxy*)-*acetophenone* (I; R = R′ = H) was obtained.

(III.) 

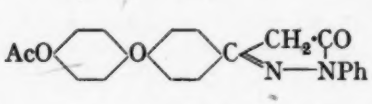
 (IV.)

The conditions used for the Ullmann condensation described above afforded a poor result when applied to the condensation between ethyl vanillate and *p*-bromoanisole. The poor yield, however, was augmented almost to theoretical by using the dry sodium derivative of the ester and applying, as catalyst, a mixture of copper bronze and anhydrous copper acetate. The subsequent methods outlined above being used, the resulting 3-*methoxy*-4-(4′-*methoxyphenoxy*)*benzoic acid* (III; R = Me, R′ = OMe, X = OH) was converted successively into 3-*hydroxy*-4-(4′-*hydroxyphenoxy*)*benzoic acid* (III; R = H, R′ = X = OH) and its *ethyl* ester (III; R = H, R′ = OH, X = OEt), 3-*acetoxy*-4-(4′-*acetoxyphenoxy*)*benzoic acid* (III; R = Ac, R′ = OAc, X = OH), ω-diazo-3-acetoxy-4-(4′-acetoxyphenoxy)acetophenone (III; R = Ac, R′ = OAc, X = CHN_2) and ω: 3-*diacetoxy*-4-(4′-*acetoxyphenoxy*)*acetophenone* (I; R = Ac, R′ = OAc). The last two stages failed to provide crystalline products, but the last-named compound was characterised by its reactions and by the *picrate* of 2 : 4′-*dihydroxy*-4-4″-*iminazolyldiphenyl ether* (IV) obtained by the action of formaldehyde and cuprammonium acetate (cf. Weidenhagen and Herrmann, *Ber.*, 1935, **68**, 1953). The keto-triol, obtained on acid hydrolysis of the triacetate, could not be obtained crystalline.

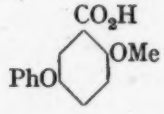
Of other known steroids, progesterone (V) bears the closest affinity to the cortical hormones and the corresponding compounds in the two series under discussion were therefore synthesised, namely, 4-(4′-hydroxyphenoxy)acetophenone (III; R = R′ = H, X = CH_3) and 3-hydroxy-4-(4′-hydroxyphenoxy)-acetophenone (III; R = H, R′ = OH, X = CH_3). 4-(4′-Acetoxyphenoxy)benzoyl chloride was condensed with ethyl sodioacetoacetate and the resulting diketo-ester was hydrolysed in two stages, first with aqueous ammonia and then with mineral acid, to give 4-(4′-*hydroxyphenoxy*)*acetophenone*



(V.)



(VI.)



(VII.)

(III; R = R′ = H, X = CH_3) in good yield. The intermediate β-keto-ester was characterised as the *phenylpyrazolone* (VI). 3-*Hydroxy*-4-(4′-*hydroxyphenoxy*)*acetophenone* (III; R = H, R′ = OH, X = CH_3) was synthesised analogously by condensation of 3-acetoxy-4-(4′-acetoxyphenoxy)benzoyl chloride with ethyl sodioacetoacetate and hydrolysis of the primary product in two stages.

It was anticipated that ketones of the type (III; R = Me, R′ = H, X = alkyl) would be accessible from 4-methoxydiphenyl ether and acyl halides by the Friedel–Crafts reaction. According to von Schickh (U.S.P. 1,717,424; B.P. 286,688) and Tomita (*J. Pharm. Soc. Japan*, 1937, **57**, 689) facile diacylation of 4-methoxydiphenyl ether in the 3- and 4′-positions occurs in the Friedel–Crafts reaction with chloroacetyl chloride, accompanied by demethylation, while, with carbonyl chloride and with benzoyl chloride, 4′-monosubstitution appears to occur (Dilthey and Harenberg, *J. pr. Chem.*, 1933, **136**, 67). It is noteworthy that in the Gattermann aldehyde synthesis substitution takes place (poor yield) in the 4′-position (Harington, *loc. cit.*), and mononitration occurs at the 3-position (Lea and Robinson, J., 1926, 411). No difficulty was experienced in introducing only one acetyl group into 4-methoxydiphenyl ether, and the homogeneous product, obtained in excellent yield, was characterised as 4-(4′-*methoxyphenoxy*)*acetophenone* (III; R = X = Me, R′ = H) by oxidation with sodium hypochlorite to 4-(4′-methoxyphenoxy)benzoic acid. It was also identical with the product obtained on methylation of 4-(4′-hydroxyphenoxy)acetophenone, which has been described above. 5-*Phenoxy*-2-*methoxybenzoic acid* (VII) was synthesised, to be available if required, as a reference compound, by Ullmann condensation of ethyl 5-bromo-2-methoxybenzoate with sodium phenoxide.

Among the compounds prepared for testing purposes was ethyl 4-(4'-hydroxyphenoxy)benzoate (III; R = R' = H, X = OEt) and it was decided to synthesise a higher homologue as well. Towards this end, 4-(4'-methoxyphenoxy)benzaldehyde (III; R = Me, R' = X = H) was condensed with malonic acid in the presence of pyridine and piperidine. The resulting 4-(4'-methoxyphenoxy)cinnamic acid was esterified with diazomethane and the *methyl* ester was reduced catalytically to *methyl* β-4-(4'-*methoxyphenoxy*)*phenylpropionate*. The latter was saponified and demethylated in one operation with hydrobromic acid to β-4-(4'-*hydroxyphenoxy*)*phenylpropionic acid*, which was then converted into the *ethyl* ester. The methods available for the synthesis of 4-(4'-methoxyphenoxy)benzaldehyde leave much to be desired, as the early ones (Harington, *loc. cit.*; Stöhr, *Z. physiol. Chem.*, 1931, **201**, 142) afforded but poor yields and a more recent one (Harington and Pitt-Rivers, *loc. cit.*), though convenient, is lengthy. An attempt was therefore made to introduce the aldehyde group directly into 4-methoxydiphenyl ether by using formomethylanilide and phosphorus oxychloride, a modern method which may be recognised as a variation of the earlier one of Dimroth and Zoeppritz (*Ber.*, 1902, **35**, 984). Only traces of aldehyde were formed, affording a semicarbazone of the expected composition and melting point.

Through the kindness of Dr. A. S. Parkes, F.R.S., ω-acetoxy-4-(4'-acetoxyphenoxy)acetophenone, 4-(4'-hydroxyphenoxy)acetophenone and 3-hydroxy-4-(4'-hydroxyphenoxy)acetophenone were examined for progesterone activity; they produced no response. Preliminary tests with ten of the above compounds have failed to demonstrate effects on glycogen deposition in the livers of fasting rats, and tests based on potassium tolerance and survival times of adrenalectomised animals have not yet been standardised; these biological aspects are being studied by Mr. H. P. Marks and Dr. F. G. Young. Quite recently, Linnell and Roushdi (*Quart. J. Pharm. Pharmacol.*, 1941, **14**, 270; *Nature*, 1941, **148**, 595) have reported signs of cortical hormone activity in two synthetic α-ketols; one of these is the simple derivative, benzoylcarbinol, which is said to have about 1/2500th, and the other, 3'-hydroxyacetyl-4-hydroxy-αβ-diethylstilbene, is stated to have rather less than 1/200th of the activity of deoxycorticosterone in prolonging the lives of young adrenalectomised rats. The present communication is intended to intimate and record our independent approach to the same objective.

Experimental.

4-(4'-*Methoxyphenoxy*)*benzoic Acid* (III; R = Me, R' = H, X = OH).—*p*-Bromoanisole (18·7 g.), ethyl *p*-hydroxybenzoate (16·6 g.), anhydrous potassium carbonate (14 g.), and copper bronze (0·9 g.) were refluxed at 200—215° (metal-bath) for 5 hours. After most of the unchanged *p*-bromoanisole had then been removed by steam-distillation, 50% aqueous potassium hydroxide (25 c.c.) was added to the mixture, which was steam-distilled for a further 15 minutes and then largely diluted with water to dissolve the potassium salt which had separated. The filtered solution was washed with ether and acidified to Congo-red with hydrochloric acid. The precipitated acid (17·1 g.), recrystallised from 60% aqueous acetic acid, afforded thin colourless plates of approximately rectangular outline, m. p. 176—177° (Found: C, 68·9; H, 4·9. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 4·9%). Harington (*loc. cit.*) records m. p. 177°. The potassium salt separated from dilute aqueous solution in minute crystals.

4-(4'-*Hydroxyphenoxy*)*benzoic Acid* (III; R = R' = H, X = OH).—The foregoing methoxy-acid (56·5 g.) was refluxed for 6 hours with a mixture (800 c.c.) of equal parts of glacial acetic acid and constant-boiling hydrobromic acid. The solution was diluted with water (1000 c.c.) and cooled. The acid which crystallised was collected and dried (49·3 g.) and a further quantity (3·2 g.) was obtained by concentrating the mother-liquor to small bulk and adding water. The *compound* separated from 50% aqueous acetic acid in flat, elongated, colourless, hexagonal prisms, m. p. 192—193° (Found: C, 67·5; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·3%). Walter (*Festschrift Emil Barell*, Basel, 1936, p. 270), giving the formula of this compound in a table, records m. p. 190°, but no other details (mode of synthesis, etc.) appear to be on record.

The *ethyl* ester, prepared by refluxing the acid (15 g.) for 6 hours with ethyl alcohol (125 c.c.) containing 5% of dry hydrogen chloride, and isolated with the aid of ether and water (yield, 16·5 g.), separated from 65% aqueous alcohol in short stout prisms, m. p. 112—113° (Found: C, 69·9; H, 5·5. $C_{16}H_{14}O_4$ requires C, 69·8; H, 5·4%).

4-(4'-*Acetoxyphenoxy*)*benzoic Acid* (III; R = Ac, R' = H, X = OH).—The hydroxy-acid (23 g.; 1 mol.) was dissolved in N-sodium hydroxide (200 c.c.; 2 mols.), cooled internally with ice, and shaken with acetic anhydride (10 c.c.; 1 mol.) for 1—2 minutes. The solution was acidified, and the precipitated *acid* extracted with ether (yield, 27·2 g.) and recrystallised from benzene, affording fine, silky, colourless, thin, flat prisms, m. p. 149—150° (Found: C, 66·4; H, 4·5. $C_{16}H_{12}O_5$ requires C, 66·2; H, 4·4%).

ω-*Diazo*-4-(4'-*acetoxyphenoxy*)*acetophenone* (III; R = Ac, R' = H, X = CHN_2).—The foregoing acetoxy-acid (26·7 g.) was refluxed in chloroform (150 c.c.) for 2½ hours with thionyl chloride (21 c.c.; *ca.* 3 mols.). Solvent and the excess of thionyl chloride were then distilled off and the last traces of the latter were entrained by distillation with two small volumes of benzene. The crude acid chloride in dry ether (120 c.c.) was added at room temperature to a dried (potassium hydroxide pellets) ethereal solution (*ca.* 500 c.c.) of diazomethane (from 60 g. of nitrosomethylurea) and the mixture was left overnight at room temperature. Filtration through a thin layer of kieselguhr to remove amorphous flocks and evaporation yielded a light orange solid (30·2 g.),

which was partly purified by recrystallisation from benzene–petrol; m. p. 111—114° (25·2 g.). The *compound* was readily soluble in warm benzene and separated on cooling in fine yellow prisms, m. p. 118—119·5° (Found: C, 64·7; H, 4·2; N, 9·7. $C_{16}H_{12}O_4N_2$ requires C, 64·8; H, 4·1; N, 9·5%):

ω-Acetoxy-4-(4′-acetoxyphenoxy)acetophenone (I; R = Ac, R′ = H).—The preceding diazo-ketone (2·05 g.; m. p. 115—117°) was warmed on the water-bath with glacial acetic acid (5 c.c.) for 1½ hours. The brown solution was mixed with ether and washed with water and sodium bicarbonate solution until free from acetic acid. The dried ethereal solution, on evaporation, yielded a light orange, crystalline solid (2·14 g.). The pure *compound* separated from methyl alcohol (norit) in colourless rectangular prisms (1·5 g.), m. p. 117·5—118° (Found: C, 65·6; H, 4·7. $C_{18}H_{16}O_6$ requires C, 65·8; H, 4·9%). The substance, on very gentle warming, readily reduced Fehling's, Benedict's (qualitative) and ammoniacal silver nitrate solutions.

ω-Hydroxy-4-(4′-hydroxyphenoxy)acetophenone (I; R = R′ = H).—A solution of the diazo-ketone (1 g.) in dioxan (10 c.c.) was warmed with 2N-sulphuric acid (6 c.c.) at 50° for ½ hour and then diluted with water. The product (0·78 g.), isolated with the aid of ether, partly crystallised and was obviously a mixture. It was refluxed with ethyl alcohol (10 c.c.) and N-hydrochloric acid (10 c.c.) for 2½ hours and worked up with ether. The brown solid (0·65 g.) isolated was boiled with much water (norit), recovered in ether, and recrystallised from small volumes of methyl alcohol. The pure *keto-diol* formed clusters of thin colourless plates, m. p. 171—172·5° (Found: C, 68·7; H, 5·0. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%). The substance readily reduced Fehling's and Benedict's (qualitative) solutions and, in the cold, ammoniacal silver solution. It was also prepared by hydrolysing the diacetate with aqueous alcoholic hydrochloric acid in the manner just described.

3-Methoxy-4-(4′-methoxyphenoxy)benzoic Acid (III; R = Me, R′ = OMe, X = OH).—Ethyl vanillate (9·8 g.; 1 mol.) was added to a solution of sodium ethoxide (from 1·2 g. of sodium; 1 atom) in absolute alcohol (40 c.c.), and the alcohol distilled away from the precipitated ethyl sodiovanillate, finally at 100°/16 mm. A mixture of the finely divided residue, copper bronze (1 g.), and anhydrous copper acetate (1 g.) (Davidson and Griswold, *J. Amer. Chem. Soc.*, 1931, **53**, 1341) was heated with *p*-bromoanisole (14 g.; 1·5 mols.) at *ca.* 240° (metal-bath) for 3 hours. The reaction mixture was cooled and distributed between water and ether. The separated ethereal solution was washed twice with cold 2N-sodium hydroxide and then with water, dried, and evaporated. The light brown oil obtained (19·5 g.) was refluxed with 6% methyl-alcoholic potassium hydroxide (100 c.c.) for 5 hours, and the reaction mixture worked up for acidic material, which was obtained as a solid (12·75 g.); this crystallised from 50% aqueous acetic acid in fine colourless prisms, m. p. 170—171° (Found: C, 65·6; H, 5·2. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%).

3-Hydroxy-4-(4′-hydroxyphenoxy)benzoic Acid (III; R = H, R′ = X = OH) *and Ethyl Ester.*—The preceding compound (9·23 g.) was refluxed for 10 hours with a mixture (240 c.c.) of equal parts of glacial acetic acid and constant-boiling hydrobromic acid, and the product (8·14 g.) isolated by concentration of the solution to small bulk under reduced pressure and dilution with water. The pure *compound* separated from 15% aqueous acetic acid (norit) in colourless hexagonal plates, m. p. 204—205° (Found: C, 63·4; H, 4·0. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1%).

The *ethyl* ester, prepared by the Fischer–Speier process in nearly quantitative yield, separated from ethyl acetate–ligroin in minute colourless rhombs, m. p. 128—129° (Found: C, 65·6; H, 5·1. $C_{15}H_{14}O_5$ requires C, 65·7; H, 5·1%).

3-Acetoxy-4-(4′-acetoxyphenoxy)benzoic Acid (III; R = Ac, R′ = OAc, X = OH).—When the above dihydroxy-acid (1 mol.) was treated with N-sodium hydroxide (3 mols.) and acetic anhydride (2 mols.), under the conditions outlined above in an analogous case, quantitative acetylation took place; the product was isolated with the aid of ether. The *substance* separated from benzene in colourless, microscopic, diamond-shaped plates, m. p. 173—174° (Found: C, 61·6; H, 4·4. $C_{17}H_{14}O_7$ requires C, 61·8; H, 4·2%).

ω : 3-Diacetoxy-4-(4′-acetoxyphenoxy)acetophenone (I; R = Ac, R′ = OAc).—The foregoing diacetoxy-acid (9·07 g.) was refluxed with freshly purified, colourless thionyl chloride (6·2 c.c.) in alcohol-free chloroform (50 c.c.) for 2½ hours. The solvent and the excess of thionyl chloride were distilled off and the last traces of the latter were entrained with benzene in the usual way. The crude acid chloride, a syrup, in dry ether (30 c. c.), was added slowly and with efficient agitation to a cold ethereal solution (*ca.* 270 c.c.) of diazomethane (from 20 g. of nitrosomethylurea), which had been dried over potassium hydroxide pellets and filtered. The solution was kept at room temperature for 18 hours, filtered from amorphous flocks, and evaporated under reduced pressure (bath not above 40°). The product did not crystallise and was therefore treated with glacial acetic acid (12 c.c.) on the water-bath for ½ hour and at the b. p. for 10 minutes. The stiff, light brown gum (10·3 g.), which was isolated in the manner described above in an analogous case, was distilled in a vacuum in small batches (*ca.* 2 g.); a stiff, pale yellow gum was obtained, b. p. approx. 255°/1·6 mm., leaving a small charred residue (Found: C, 62·3; H, 4·9. $C_{20}H_{18}O_8$ requires C, 62·2; H, 4·7%). The distilled product readily reduced Fehling's and Benedict's (qualitative) solutions and, slowly in the cold and rapidly on gentle warming, ammoniacal silver solution.

The substance was characterised as the *picrate* of *2 : 4′-dihydroxy-4-4″-iminazolyldiphenyl ether* (IV) as follows: the gum (2·5 g.) in 60% aqueous alcohol (50 c.c.) was treated with copper acetate (1·4 g., anhydrous), 40% formalin solution (1·5 c.c.), and 25% aqueous ammonia (10 c.c.) on the water-bath (cf. Weidenhagen and Herrmann, *loc. cit.*). The copper derivative which separated (1·8 g.) was collected, dried, and freed from copper in boiling water with hydrogen sulphide. The filtered solution, after cooling, was separated from a brown amorphous precipitate, evaporated to small bulk, and treated with an excess of aqueous picric acid. The

picrate which separated gradually became crystalline; it was recrystallised several times from (approx.) 40% aqueous methyl alcohol, forming orange rhombs, which effervesced at 128—130°, resolidified in prisms, and melted finally at 183—184° (Found: loss at 140° in a high vacuum over phosphoric oxide, 5·0. Found for anhydrous material: C, 51·1; H, 3·4; N, 14·3. $C_{15}H_{12}O_3N_2,C_6H_3O_7N_3,1{\cdot}5H_2O$ requires H_2O, 5·2%. $C_{15}H_{12}O_3N_2,C_6H_3O_7N_3$ requires C, 50·7; H, 3·0; N, 14·1%).

4-(4'-Hydroxyphenoxy)acetophenone (III; R = R' = H, X = CH_3).—4-(4'-Hydroxyphenoxy)benzoic acid (23 g.; 1 mol.) was acetylated and treated with thionyl chloride as described above. The acid chloride, dissolved in benzene (50 c.c.), was added to ethyl sodioacetoacetate (2 mols., from 26 g. of ethyl acetoacetate and 4·6 g. of powdered sodium) in benzene (300 c.c.). The mixture was refluxed for 3½ hours and then left at room temperature for 48 hours. The precipitated yellow sodium derivative was collected and washed with ether (yield, 32·9 g.; theo., 36·4 g.).

The sodium derivative was dissolved in water (100 c.c.) and warmed on the water-bath with ammonium chloride (5·5 g.) and 12% aqueous ammonia (20 c.c.) for 20 minutes. The heavy oil that separated was recovered in ether and the extract, after being washed with water and dilute sulphuric acid, was evaporated, finally at 100°/22 mm., yielding a stiff, light yellow, clear syrup (22·9 g.). This product gave a port-wine colour in alcoholic solution with a drop of aqueous ferric chloride and was characterised as the *phenylpyrazolone* (VI). The syrup (0·26 g.) and freshly distilled phenylhydrazine (0·1 c.c.) were heated on the water-bath for 3 hours. The resulting light brown gum solidified on trituration with ether; after being washed with ether (yield, 0·2 g.), it separated from 60% aqueous acetic acid as a colourless micro-crystalline powder, m. p. 128·5—130° (Found: C, 71·9; H, 4·8; N, 7·2. $C_{23}H_{18}O_4N_2$ requires C, 71·5; H, 4·7; N, 7·2. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·6; N, 8·1%). The analysis showed that the acetyl group had not been lost.

The remainder of the keto-ester (22·5 g.) was refluxed with 10% sulphuric acid (100 c.c.) for 5½ hours. The product was extracted with ether, washed with sodium bicarbonate solution, dried, and recovered (yield, 16·3 g.; over-all yield, 73%). The *substance* separated from 60% aqueous methyl alcohol in colourless plates, m. p. 155—156° (Found: C, 73·4; H, 5·2. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%).

3-Hydroxy-4-(4'-hydroxyphenoxy)acetophenone (III; R = H, R' = OH, X = CH_3).—3-Acetoxy-4-(4'-acetoxyphenoxy)benzoic acid (11·5 g.) was converted into the acid chloride with thionyl chloride (10 c.c.) in the usual way. The crude chloride, freed from the excess of thionyl chloride, was added in benzene (50 c.c.) to ethyl sodioacetoacetate (from 9·2 c.c. of ethyl acetoacetate and 1·6 g. of powdered sodium) in benzene (100 c.c.). The solution became clear and it was refluxed for 4½ hours. No separation of the sodio-derivative of the product occurred in this case and the reaction mixture was worked up by treatment with excess of dilute sulphuric acid. Evaporation of the benzene solution, finally at 100°/18 mm., yielded a light brown, viscous syrup (20 g.).

Although the presence of ammonium chloride was not theoretically necessary for the first stage of the hydrolysis in this case, it was nevertheless added, since it has been established empirically that the use of ammonium chloride, together with ammonia, is beneficial in hydrolyses of this type (cf. Shriner and Schmidt, *J. Amer. Chem. Soc.*, 1929, **51**, 3636). The crude diketo-ester was shaken with water (50 c.c.), ammonium chloride (6 g.), and 12% aqueous ammonia (15 c.c.) at 45—50° for 10 minutes. The heavy oil which separated was recovered with the aid of ether and isolated as a reddish-brown syrup (15·9 g.), giving a typical blood-red colour in alcoholic solution with a drop of aqueous ferric chloride. The crude product was at once refluxed with 10% sulphuric acid (100 c.c.) for 6 hours. The product was distributed between water and ether, and the ethereal solution washed with sodium bicarbonate solution. The product was removed from the ether by three washings with 2N-sodium hydroxide, and recovered by acidification and extraction with ether. Evaporation of the ether afforded a dark brown gum (7·2 g.). Treatment in boiling 40% aqueous methyl alcohol with norit and recovery by means of ether extraction gave a light golden-yellow glass (5·9 g.). The *compound* separated from ethyl acetate–ligroin (1 : 2) as a colourless microcrystalline powder, m. p. 149—150·5° (Found: C, 68·6; H, 5·1. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%).

The 2 : 4-*dinitrophenylhydrazone* separated from alcohol in deep orange-red sheaves, m. p. 234° (Found: N, 13·4. $C_{20}H_{16}O_7N_4$ requires N, 13·2%).

Friedel–Crafts Reaction between 4-Methoxydiphenyl Ether and Acetyl Chloride. 4-(4'-Methoxyphenoxy)-acetophenone (III; R = X = CH_3, R' = H).—(A) 4-Methoxydiphenyl ether was prepared by treating dry sodium phenoxide with *p*-bromoanisole in the presence of copper bronze and copper acetate in the manner outlined above (yield, 70%; b. p. 166°/16 mm.). It (10 g.; 1 mol.) was treated in carbon disulphide (50 c.c.) containing acetyl chloride (3·7 c.c.; 1 mol.) with successive portions of finely powdered aluminium chloride (total, 13·3 g.; 2 mols.) at room temperature. The reaction was very vigorous and two liquid layers formed. After an hour at room temperature and 10 minutes at 40°, the carbon disulphide was decanted, and the deep red lower layer poured on ice. The product crystallised as a faintly pink solid. It was taken up in ether, washed twice with 2N-sodium hydroxide and once with dilute sulphuric acid, dried, and recovered as a viscous syrup (11·4 g., 94%), which rapidly crystallised on cooling, m. p. 49—53°. Distillation under diminished pressure (b. p. approx. 233°/16 mm.) raised the m. p. to 54—56°. The *compound* was finally obtained in sheaves of colourless plates, m. p. 60—61°, by recrystallisation from ligroin (Found: C, 74·3; H, 5·8; OMe, 12·8. $C_{15}H_{14}O_3$ requires C, 74·4; H, 5·8; OMe, 12·8%).

The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in microscopic crimson prisms, m. p. 171° (Found: C, 59·6; H, 4·2; N, 13·4. $C_{21}H_{16}O_6N_4$ requires C, 59·7; H, 4·3; N, 13·3%).

(B) 4-(4′-Hydroxyphenoxy)acetophenone (0·5 g.) in 35% potassium hydroxide solution (40 c.c.) was treated with four portions of methyl sulphate (each of 2 c.c.), with shaking and cooling. The oil which separated crystallised at room temperature. The mixture was finally heated on the boiling water-bath for 5 minutes, cooled, and extracted with ether. The extract was washed with 2N-sodium hydroxide, dried, and evaporated, yielding a colourless viscous syrup (0·51 g.) which rapidly crystallised, m. p. 55—56°, raised to 59° by recrystallisation from ligroin. Sublimation at 16 mm. (bath, 190°) raised the m. p. to 60—61°, alone and in admixture with the product obtained in (A) (Found: C, 74·5; H, 5·8%).

Oxidation of Preceding Compound with Sodium Hypochlorite. 4-(4′-*Methoxyphenoxy*)*benzoic Acid.*—The foregoing ketone (1 g.), prepared as in (A), was refluxed with 2·5% sodium hypochlorite solution (85 c.c.) for 2 hours; the oil rapidly dissolved. The excess of oxidant was destroyed with sodium sulphite. On cooling, the characteristic, sparingly soluble sodium salt separated and was kept in solution by dilution with water. The solution was washed with a small volume of ether, and the free acid (0·91 g.; m. p. 175—177°) was recovered, *via* ether, in the normal way. Recrystallisation from 60% aqueous acetic acid afforded 4-(4′-methoxyphenoxy)-benzoic acid in its characteristic crystalline habit, m. p. 177°, alone and in admixture with an authentic sample (Found: C, 68·7; H, 5·0. Calc. for $C_{14}H_{12}O_4$: C, 68·8; H, 4·9%).

Ethyl 5-Phenoxy-2-methoxybenzoate.—(i) 5-Bromosalicylic acid (40·6 g.) (Hewitt, Kenner, and Silk, J., 1904, **85**, 1228) in methyl alcohol (120 c.c.) was methylated with 50% potassium hydroxide solution and methyl sulphate (total, 57 c.c.) and the product was isolated as the methoxy-acid (40·3 g.), which crystallised from 50% aqueous acetic acid in fine needles (35·5 g.), m. p. 111—112·5° (lit., m. p. 119°). Esterification by the Fischer–Speier process (75 c.c. of 6% ethyl-alcoholic hydrogen chloride; 6 hours' refluxing) yielded the ethyl ester (35·1 g.) as a colourless limpid oil, b. p. 179°/21 mm.

(ii) A mixture of the foregoing ethyl 5-bromo-2-methoxybenzoate (35 g.) and dry sodium phenoxide (from 15 g. of phenol and 3·2 g. of sodium in absolute alcohol) was heated at 230° (metal-bath) with copper bronze (0·5 g.) and anhydrous copper acetate (0·5 g.) for 5½ hours, cooled, and distributed between ether and water. After filtration, the separated ethereal layer was washed with cold 3N-sodium hydroxide and with dilute sulphuric acid, dried, and fractionated. The limpid brown oil distilled almost entirely at 215—230°/18 mm. Further fractionation gave: (*a*) b. p. to 210°/18 mm. (5·4 g.); (*b*) a colourless limpid oil (19·8 g., 54%), b. p. 225—232°/18 mm., fairly steady at 227°/18 mm. (Found: C, 70·2; H, 5·8. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%). The second fraction subsequently crystallised and the *substance* then separated from petrol in clusters of colourless, approximately rectangular plates, m. p. 63°.

5-Phenoxy-2-methoxybenzoic Acid (VII).—The preceding compound (2·53 g.) was quantitatively saponified by refluxing with absolute alcohol (5 c.c.) and 50% aqueous potassium hydroxide (5 c.c.) for several hours. The free *acid*, recovered by means of ether, separated from 65% aqueous acetic acid in small, colourless, hexagonal plates, m. p. 108·5—110° (Found: C, 68·7; H, 4·8. $C_{14}H_{12}O_4$ requires C, 68·8; H, 4·9%).

4-(4′-*Methoxyphenoxy*)*cinnamic Acid.*—Crude 4-(4′-methoxyphenoxy)benzaldehyde (7·6 g.) (Harington and Pitt-Rivers, *loc. cit.*), dissolved in pyridine (40 c.c.), was treated with malonic acid (3·7 g.) and piperidine (10 drops). The mixture was warmed over a free flame to initiate reaction and then left on the water-bath for an hour. To ensure complete reaction, more malonic acid (1·9 g.) was added and the mixture was boiled for 10 minutes. When it was poured into water, a microcrystalline solid separated. The product was taken up in ether and freed from pyridine by washing with water and zinc chloride solution. The crude product was a light yellow, somewhat sticky, solid (7·95 g., 88%) and separated from 60% aqueous acetic acid in thin colourless plates, m. p. 176—177° (Found: C, 71·1; H, 5·2. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%). Harington (*loc. cit.*) records m. p. 175·5°.

The sparingly soluble *methyl* ester, obtained by the action of an excess of diazomethane, separated from methyl alcohol in thin colourless plates, m. p. 129—130° (Found: C, 72·0; H, 5·6. $C_{17}H_{16}O_4$ requires C, 71·8; H, 5·6%).

Methyl β-4-(4′-*Methoxyphenoxy*)*phenylpropionate.*—The preceding unsaturated ester (4·7 g.) was dissolved in warm ethyl acetate (90 c.c., which barely sufficed for solution at room temperature), and hydrogenated in the presence of 2% palladised strontium carbonate (5 g.) with hydrogen under slight pressure (*ca.* 2 feet of water). After the lag period (20 minutes), rather more than the required volume of hydrogen was absorbed in about 10 minutes (corrected observed vol. 425 c.c.; theo., 371 c.c.). The solution was filtered and evaporated, the product crystallising promptly on removal of the solvent. The saturated *ester* was more soluble than its precursor, and separated from methyl alcohol in thin rhomboid plates, m. p. 55—56° (Found: C, 71·1; H, 6·2. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%).

β-4-(4′-*Hydroxyphenoxy*)*phenylpropionic Acid and Ethyl Ester.*—The foregoing hydrogenation product (4·5 g.) was refluxed for 6½ hours with a mixture (60 c.c.) of equal parts of glacial acetic acid and constant-boiling hydrobromic acid. The product (3·75 g.) separated in a pure condition on dilution with water. The *acid* separated from 30% aqueous acetic acid in radiating clusters of fine colourless needles, m. p. 161° (Found: C, 69·8; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

The *ethyl* ester, obtained in practically quantitative yield by the Fischer–Speier process, was a colourless viscous syrup, b. p. 225—230°/2·2 mm. (Found: C, 71·8; H, 6·5. $C_{17}H_{18}O_4$ requires C, 71·3; H, 6·3%), which subsequently crystallised spontaneously; it then separated from ligroin, containing a small proportion of ethyl acetate, in colourless, well-developed prisms, m. p. 76—77°.

Attempted Preparation of 4-(4′-*Methoxyphenoxy*)*benzaldehyde from* 4-*Methoxydiphenyl Ether and Formo-*

methylanilide. 4-(4′-*Methoxyphenoxy*)*benzaldehyde Semicarbazone.*—4-Methoxydiphenyl ether (10 g.) was treated with formomethylanilide (9 g.), and phosphorus oxychloride (6·1 c.c.) on the boiling water-bath for 6 hours (cf. β-naphthyl methyl ether, *Organic Syntheses*, 1940, **20**, 11). The product, isolated by pouring into ice-water and extraction with ether, gave a positive test for carbonyl with Brady's reagent. Vacuum distillation, however, gave largely unchanged starting material (judged by the b. p.), and only a small higher-boiling fraction (*ca.* 0·9 g.), b. p. 170—190°/16 mm. The latter fraction, treated with semicarbazide hydrochloride (0·45 g.) and sodium acetate (0·55 g.) in aqueous alcohol on the water-bath for several hours, yielded a semicarbazone (0·1 g.), m. p. 211—214°, recrystallisation of which from *n*-butyl alcohol afforded colourless plates, m. p. 215° (Found: C, 62·5; H, 5·4; N, 14·4. Calc. for $C_{15}H_{15}O_3N_3$: C, 63·2; H, 5·2; N, 14·7%). Harington and Pitt-Rivers (*loc. cit.*) record m. p. 212—213°.

I am indebted to Mr. H. P. Marks and Dr. F. G. Young for their courtesy in communicating their original observations to me and for the opportunity to undertake the work described. Mr. L. V. Sharp assisted in the preparation of starting materials.

National Institute for Medical Research, Hampstead, London, N.W.3. [*Received, December 19th*, 1941].

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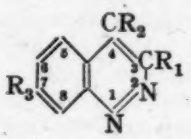
58. *Cinnolines. Part I. Some New Examples.*

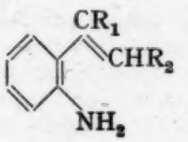
By James C. E. Simpson and Oliver Stephenson.

The syntheses are described of 6-*bromo*-4-*phenyl*-, 6-*chloro*-4-(4′-*hydroxyphenyl*)-, and 6-*chloro*-4-(2′-*hydroxy*-5′-*methylphenyl*)-*cinnoline* by the Stoermer reaction [cyclisation of diazotised α-(2-*aminophenyl*)-α-*arylethylenes*]. During the course of the work a number of new benzophenone derivatives have been prepared.

The chemistry of cinnoline compounds has received scant attention since the discovery, nearly sixty years ago, of the first derivatives, 4-hydroxycinnoline-3-carboxylic acid (I; $R_1 = CO_2H$, $R_2 = OH$, $R_3 = H$) (von Richter, *Ber.*, 1883, **16**, 677) and 4-methylcinnoline-7-carboxylic acid (I; $R_1 = H$, $R_2 = Me$, $R_3 = CO_2H$) (Widman, *Ber.*, 1884, **17**, 722). Cinnoline itself (I; $R_1 = R_2 = R_3 = H$) was prepared from the former acid some years later by Busch and Rast (*Ber.*, 1897, **30**, 521). A discouraging factor in this field has doubtless been the lack of a convenient method of preparation, in contrast to the isomeric phthalazines, which are readily accessible and have in consequence been widely studied. A somewhat easier route to the cinnoline ring system than the method of von Richter, which involved cyclisation of diazotised *o*-aminophenylpropiolic acid, was explored by Stoermer and Fincke (*Ber.*, 1909, **42**, 3115). Employing the reaction originally discovered by Widman (*loc. cit.*), namely, the cyclisation of diazotised *o*-aminoarylethylenes, these authors showed that α-(2-aminophenyl)-α-arylethylenes (II; R_1 = aryl, $R_2 = H$), on treatment with nitrous acid in presence of hydrochloric acid, passed smoothly and spontaneously into the corresponding 4-arylcinnolines (I; $R_1 = R_3 = H$, R_2 = aryl).



(I.)



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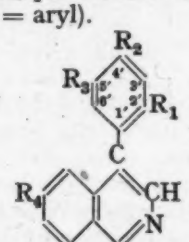


(III.)

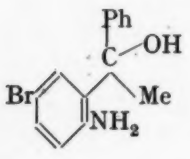
4-Phenyl-, 4-phenyl-3-methyl-, and 4-*p*-tolyl-cinnoline were synthesised by this means, the requisite diarylethylenes being obtained from the appropriate diaryl ketones and a Grignard reagent, followed by dehydration of the resulting carbinols. Later, Stoermer and Gaus (*Ber.*, 1912, **45**, 3104) prepared 4-*p*-anisyl- and 4-*p*-hydroxyphenyl-cinnoline, the latter by demethylation of the former. Stoermer and Fincke observed also that the substitution of bromine for hydrogen on the β-ethylenic carbon atom of (II) tended to inhibit the cyclisation of the diazonium salt, (II; $R_1 = Ph$, $R_2 = Br$) giving only 4-phenylcinnoline in poor yield; but (apart from Widman's acid) the influence on ring closure of strongly polar substituents in either of the two aryl nuclei has not been studied.

In this paper we describe the syntheses of 6-*bromo*-4-*phenyl*-4-*cinnoline* (III; $R_1 = R_2 = R_3 = H$, $R_4 = Br$), 6-*chloro*-4-(4′-*hydroxyphenyl*)*cinnoline* (III; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Cl$), and 6-*chloro*-4-(2′-*hydroxy*-5′-*methylphenyl*)*cinnoline* (III; $R_1 = OH$, $R_2 = H$, $R_3 = Me$, $R_4 = Cl$) by the Stoermer reaction. The yields, based on the diarylethylenes, were in all cases reasonably high, so the

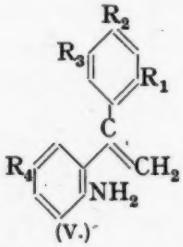
scope of this method for the synthesis of cinnolines containing substituted aryl nuclei is in all probability fairly wide.

Condensation of 5-bromo-2-aminobenzophenone (Angel, J., 1912, **101**, 515) with methylmagnesium iodide gave *phenyl-(5-bromo-2-aminophenyl)methylcarbinol* (IV), which was smoothly dehydrated by sulphuric acid to the ethylene (V; $R_1 = R_2 = R_3 = H$, $R_4 = Br$). The latter was an oil, characterised by the formation of two crystalline, easily hydrolysable sulphates, each of which on basification and benzoylation furnished the same *benzamido*-compound, m. p. 114°. A solution of the free amino-ethylene in dilute sulphuric acid was immediately converted into the cinnoline (III; $R_1 = R_2 = R_3 = H$, $R_4 = Br$), m. p. 144°, by addition of sodium nitrite.

For the synthesis of (III; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Cl$), we utilised the observation of Zincke and Siebert (*Ber.*, 1906, **39**, 1930) that *o*-nitrobenzaldehyde and phenol condense in the presence of dry hydrogen chloride to the anthroxan (VI; $R_1 = R_3 = H$, $R_2 = OH$), which on reduction yields 5-chloro-2-amino-4'-hydroxybenzophenone (VII; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = NH_2$). In our hands the conditions employed for this reduction by Zincke and Siebert (tin and hydrochloric acid) proved unsatisfactory, but the use of iron and acetic acid gave excellent yields of the ketone. The carbinol formed by treatment of the latter compound with methylmagnesium iodide underwent spontaneous dehydration to the *diarylethylene* (V; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Cl$); this was isolated in high yield, and was characterised by the preparation of a *dibenzoyl* derivative. Addition of aqueous sodium nitrite to a solution of the amino-ethylene in hydrochloric acid gave a 70% yield of the cinnoline (III; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Cl$), but in dilute sulphuric acid the yield was lower (50%) and accompanied by partial resinification.



(IV.)



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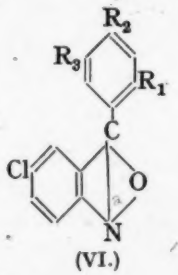

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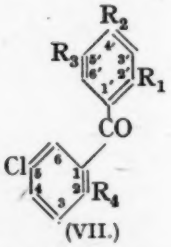

(VII.)

Condensation of *o*-nitrobenzaldehyde, hydrogen chloride, and *p*-cresol yields the anthroxan (VI; $R_1 = OH$, $R_2 = H$, $R_3 = Me$) (Zincke and Siebert, *loc. cit.*), reduction of which to the corresponding amino-ketone proceeded smoothly, as in the former case, with iron and acetic acid, but was unsatisfactory when tin and hydrochloric acid were used. The product resulting from treatment of the amino-ketone with the methyl Grignard reagent was a resin which resisted all attempts at crystallisation. In an early effort to isolate the amino-ethylene (or amino-carbinol), it was found that benzoylation of the resin furnished a crystalline *dibenzoyl* derivative, m. p. 119°, of the amino-ethylene (V; $R_1 = OBz$, $R_2 = H$, $R_3 = Me$, $R_4 = Cl$, NHBz for NH_2). This substance was accordingly hydrolysed in the expectation of obtaining the free amino-ethylene, since the parent amino-ketone had been found to be recoverable by a similar hydrolysis of its *dibenzoyl* compound. However, the product of hydrolysis of the compound, m. p. 119°, was a resin, which on rebenzoylation gave a new *benzoyl* derivative, m. p. 235°; this appeared from analysis to have the formula $C_{36}H_{26}O_4NCl$, and we therefore regard it as a tribenzoyl derivative (V; $R_1 = OBz$, $R_2 = H$, $R_3 = Me$, $R_4 = Cl$, NBz_2 for NH_2). The compound was not investigated further, for the isolation of the pure *amino-ethylene* (V; $R_1 = OH$, $R_2 = H$, $R_3 = Me$, $R_4 = Cl$) had in the meantime been achieved through the crystalline *hydrochloride*, which was converted into the cinnoline (III; $R_1 = OH$, $R_2 = H$, $R_3 = Me$, $R_4 = Cl$) in the usual manner.

The orientations of the three new cinnolines are obviously dependent on those of the related ketones, and in the case of the two phenolic ketones [(VII; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = NH_2$), m. p. 178°, and (VII; $R_1 = OH$, $R_2 = H$, $R_3 = Me$, $R_4 = NH_2$), m. p. 114°] no rigid proof of structure appears to exist. By means of the procedure described below, we have been able to establish the correctness of the constitutions assigned to these ketones in so far as the positions of the chlorine atoms are concerned.

Zincke and Siebert (*loc. cit.*) describe the conversion of the ketone, m. p. 178°, into 3-chloro-4'-hydroxybenzophenone, a result which we have in part confirmed by oxidation of this substance to *m*-chlorobenzoic acid. 3-Chloro-4'-hydroxybenzophenone, however, could also arise from the ketone, m. p. 178°, if the latter were represented by an alternative structure with the chlorine atom on C_3 instead of C_5. We have eliminated this possibility by conversion of the ketone into 2 : 5-*dichloro-4'-hydroxybenzophenone*, the orientation of the halogen-substituted ring being proved by oxidation to 2 : 5-dichlorobenzoic acid. The position of the chlorine atom in the second amino-ketone (m. p. 114°) was similarly established by

transformation of the ketone into 2 : 5-*dichloro*-2'-*hydroxy*-5'-*methylbenzophenone*, followed by oxidation of the latter to 2 : 5-dichlorobenzoic acid. Incidentally, the preparation of these dichloro-ketones contradicts the experience of Zincke and Siebert, who were unable to prepare any derivatives of the diazotised amino-ketones except 3-chloro-4'-hydroxybenzophenone (the recorded m. p. of which is considerably lower than that found by us).

In an attempt to establish the position of the phenolic group in each of the amino-ketones, we prepared the *methyl* ethers of the two anthroxans [(VI; $R_1 = R_3 = H$, $R_2 = OMe$) and (VI; $R_1 = OMe$, $R_2 = H$, $R_3 = Me$)], and reduced these to the corresponding *amino-ketones*. On the assumption that the positions assigned to the phenolic groups in the anthroxans are correct it was anticipated that oxidation of the methoxy-amino-ketones would furnish anisic acid and 4-methoxy*iso*phthalic acid respectively. However, the ketone from (VI; $R_1 = OMe$, $R_2 = H$, $R_3 = Me$) was incompletely oxidised by alkaline permanganate, and no crystalline product could be obtained when the oxidation was continued in acid solution. In view of this result, the ketone from (VI; $R_1 = R_3 = H$, $R_2 = OMe$) was diazotised with a view to obtaining a phenol more amenable to oxidation, but, in spite of several trials, almost the whole of the product was an alkali-insoluble resin, and only a trace of crystalline phenol could be obtained.

It is our intention to develop this preliminary work when an opportunity occurs.

Experimental.

(Melting points are uncorrected.)

Phenyl-(5-bromo-2-aminophenyl)methylcarbinol (IV).—An ethereal solution of methylmagnesium iodide prepared from 2 g. of magnesium and 12 g. of methyl iodide was treated with a similar solution of 5-bromo-2-aminobenzophenone (5 g., m. p. 110°, prepared by the method of Angel, *loc. cit.*, who gives m. p. 111°), added slowly with cooling. The resultant deep red solution was refluxed for 1 hour, solid material separating. The product was decomposed with ice and dilute hydrochloric acid, and the ethereal solution dried over sodium sulphate and evaporated. The residue, which rapidly solidified, was recrystallised from ether–ligroin (b. p. 40—60°), yielding pale yellow, thick prisms of the *carbinol*, m. p. 100° (Found: C, 58·3, 58·5; H, 5·05, 5·1; N, 5·05. $C_{14}H_{14}ONBr$ requires C, 57·5; H, 4·8; N, 4·8%). The high values for carbon are possibly attributable to the facility with which the carbinol undergoes dehydration, this explanation being supported by the facts that the *N*-acetyl and the *N*-benzoyl derivative give similar high values, whereas the *N*-benzoyl ethylene (*q.v.*) gives satisfactory analytical data.

The N-*acetyl* derivative of the carbinol was prepared by treatment of the latter in excess of pyridine with acetic anhydride at room temperature. After 4 days the solution was diluted with water, and the acetamido-compound recrystallised from aqueous methanol, forming cream-coloured, long, prismatic needles, m. p. 181—182° (Found: C, 58·4; H, 4·5. $C_{16}H_{16}O_2NBr$ requires C, 57·5; H, 4·8%). The N-*benzoyl* derivative (from pyridine and benzoyl chloride) separated from aqueous alcohol in colourless prisms, m. p. 196° (Found: C, 64·4; H, 4·6. $C_{21}H_{18}O_2NBr$ requires C, 63·6; H, 4·6%).

Derivatives of α-Phenyl-α-(5-bromo-2-aminophenyl)ethylene.—(i) After the foregoing carbinol (0·5 g.) had been refluxed for 2½ hours with 4N-sulphuric acid (60 c.c.), white feathery crystals, m. p. 107°, separated on cooling (Found: C, 40·6; H, 5·2. $C_{14}H_{12}NBr,H_2SO_4,2H_2O$ requires C, 41·2; H, 4·4%). This *sulphate* was extremely hygroscopic and somewhat unstable, being slowly decomposed in cold water, and rapidly in hot, to the free amino-ethylene.

(ii) Treatment of the carbinol with 2N-sulphuric acid under identical conditions yielded a second sulphate of the amino-ethylene; this salt crystallised from the acid solution in fine white needles, m. p. 154°. Although this compound appeared to be rather more stable than the sulphate, m. p. 107°, it likewise decomposed slowly in aqueous solution.

(iii) Each of the above sulphates was shaken with aqueous-alcoholic ammonia, and the base was isolated by extraction with ether. In each case the uncrystallisable oil obtained was identified as the same diaryl-ethylene by benzoylation (benzoyl chloride and pyridine), *α-phenyl-α-(5-bromo-2-benzamidophenyl)ethylene* separating in each instance from aqueous methanol in colourless prismatic needles, m. p. and mixed m. p. 113·5—114° (Found: C, 67·0; H, 4·3. $C_{21}H_{16}ONBr$ requires C, 66·65; H, 4·2%).

6-Bromo-4-phenylcinnoline.—A solution of the sulphate (0·4 g.), m. p. 150°, in warm dilute sulphuric acid was cooled to 10° and treated with solid sodium nitrite (0·1 g.). The crystalline *cinnoline*, which separated almost immediately in nearly quantitative yield, was recrystallised from aqueous alcohol containing ammonia and subsequently from ether–ligroin or slightly aqueous methanol. It formed yellow, light, silky needles, m. p. 143·5—144·5°. The same result was obtained when the addition of sodium nitrite was carried out at 40° (Found: C, 59·7, 59·9, 59·9; H, 3·1, 3·0, 3·5; N, 9·6; Br, 26·9. $C_{14}H_9N_2Br$ requires C, 58·95; H, 3·2; N, 9·8; Br, 28·0%). No explanation can be advanced in respect of the high carbon values, which were obtained with three different samples. A solution of the cinnoline in concentrated hydrochloric acid gave an amorphous insoluble chloroplatinate, and benzene solutions of the base and picric acid gave a crystalline picrate, m. p. 270—275° (decomp.). The base showed no tendency to form a sulphate in aqueous solution.

5-Chloro-2-amino-4'-hydroxybenzophenone (VII; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = NH_2$)—The anthroxan prepared from *o*-nitrobenzaldehyde and phenol had m. p. 240—241° after crystallisation from alcohol (Zincke

and Siebert, *loc. cit.*, give m. p. 241°). The reduction was carried out by addition of iron filings (5 g.) to a suspension of the powdered anthroxan (10 g.) in glacial acetic acid (200 c.c.) heated on the water-bath. After the anthroxan had dissolved (¼ hour), the solution was diluted with water (50 c.c.), and a further quantity of iron filings (10 g.) added in five equal portions during 2 hours with frequent shaking. After a further ½ hour the solution was treated with water (50 c.c.), filtered from inorganic matter, and diluted with water until crystallisation occurred in the hot. After several crystallisations from aqueous methanol the amino-ketone formed yellow, flattened needles, m. p. 177—178° (lit., m. p. 174°); yield (pure), 70%. The *dibenzoyl* derivative, m. p. 143°, was comparatively sparingly soluble, and separated from rectified spirit in colourless needles (Found: C, 70·6; H, 3·8. $C_{27}H_{18}O_4NCl$ requires C, 71·1; H, 4·0%).

3-Chloro-4'-hydroxybenzophenone (VII; $R_1 = R_3 = R_4 = H$, $R_2 = OH$).—The foregoing amino-ketone (1 g.) was dissolved in absolute alcohol (15 c.c.) and treated successively with concentrated sulphuric acid (1 c.c.) and amyl nitrite (5 c.c.), added at 10° with shaking. After 5 minutes the solution was warmed somewhat, and when the reaction had subsided the solution was refluxed for 5 minutes, diluted with water, and extracted with ether. The extract was washed with water and with 4% sodium hydroxide solution; the latter was then acidified with hydrochloric acid, and the free phenol extracted with ether. The crude product was crystallised several times from aqueous methanol (charcoal), from which the phenol separated in fluffy, somewhat discoloured needles, m. p. 169·5—171° (Zincke and Siebert, *loc. cit.*, describe the compound as colourless needles, m. p. 161°); yield, approx. 50% (Found: C, 67·2; H, 4·1. Calc. for $C_{13}H_9O_2Cl$: C, 67·1; H, 3·9%). The phenol dissolved easily in warm aqueous sodium carbonate.

Oxidation of the phenol in alkaline potassium permanganate solution gave *m*-chlorobenzoic acid, m. p. 153—155° after crystallisation from hot water.

2 : 5-Dichloro-4'-hydroxybenzophenone (VII; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Cl$).—5-Chloro-2-amino-4'-hydroxybenzophenone (1 g.) was warmed with glacial acetic acid (20 c.c.) and concentrated hydrochloric acid (1·5 c.c.), water (5 c.c.) being added to obtain complete solution. Diazotisation was effected at 5° with a solution of sodium nitrite (0·4 g.) in water (20 c.c.), starch–iodide paper being used as indicator. The clear solution was added during 10 minutes to a hot solution of cuprous chloride (2 g.) in concentrated hydrochloric acid (20 c.c.) and water (20 c.c.). The resultant suspension was boiled for 5 minutes, filtered cold, and the crude product recrystallised from aqueous methanol (charcoal), from which the *dichloro-phenol* separated in dense, brittle, yellow prisms, m. p. 171—172·5°; yield, 80%. The compound gave a deep brown solution with ferric chloride in alcohol, and dissolved in aqueous sodium carbonate (Found: C, 58·6; H, 2·9; Cl, 27·1. $C_{13}H_8O_2Cl_2$ requires C, 58·4; H, 3·0; Cl, 26·6%).

In one of a number of preliminary attempts to prepare the above compound from the amino-benzophenone, the amount of sodium nitrite added was not rigidly controlled, but the other conditions were as described above. The major crystalline product in this case was a poor yield of a *substance* which crystallised from aqueous methanol in canary-yellow, hair-like needles, m. p. 224—226° (Found: N, 5·7; Cl, 15·8%).

Oxidation of 2 : 5-Dichloro-4'-hydroxybenzophenone.—A solution of the phenol (400 mg.) in 0·2N-sodium carbonate (20 c.c.) was mixed with 2% potassium permanganate solution (75 c.c.) and left over-night at 40—45°. The solution was filtered, concentrated, and acidified, and the precipitate collected. Some unchanged phenol (*ca.* 50 mg.) was removed by dissolving the crude product in ether and extracting the acid fraction with aqueous bicarbonate. The purified acid, after crystallisation from hot water, formed needles (150 mg.), m. p. 153—154° both alone and when mixed with authentic 2 : 5-dichlorobenzoic acid prepared by the method of Crauw (*Rec. Trav. chim.*, 1931, **50**, 753). The identity of the acid was confirmed by the preparation of the m-*nitroanilide* (*via* the acid chloride in pyridine solution); this derivative separated from aqueous methanol in colourless needles, m. p. 151—152° both alone and when mixed with an authentic specimen (Found: N, 9·0; Cl, 22·4. $C_{13}H_8O_3N_2Cl_2$ requires N, 9·0; Cl, 22·8%).

5-Chloro-2-amino-4'-methoxybenzophenone (VII; $R_1 = R_3 = H$, $R_2 = OMe$, $R_4 = NH_2$).—5 G. of the anthroxan, m. p. 239—240°, were added to a solution of sodium (0·6 g.) in methanol (50 c.c.). The clear orange solution which soon formed was treated with a large excess (10 c.c.) of methyl iodide and heated under reflux. After ½ hour, crystalline material separated; this was redissolved by addition of benzene (25 c.c.), and refluxing continued for a further 3 hours. The solution was then concentrated, water added, and the whole extracted with ether. The extract was washed with dilute sodium hydroxide solution and water, dried, and evaporated. Crystallisation of the residue from acetone gave long, brittle, yellow needles (4·5 g.) of the *chloromethoxyanthroxan*, m. p. 143—145° (Found: C, 65·35; H, 4·25. $C_{14}H_{10}O_2NCl$ requires C, 64·7; H, 4·0%).

The above compound (4 g.) was dissolved in glacial acetic acid (40 c.c.) and reduced with iron filings (6 g.), as described for the methoxyanthroxan, m. p. 98° (*q.v.*), for 2½ hours. The product was isolated and crystallised first from aqueous methanol and then from a small volume of absolute methanol, from which the *amino-ketone* (3·5 g.) separated in dense yellow rhombs or prisms, m. p. 100—101° (Found: C, 64·1, 64·4; H, 4·9, 4·6. $C_{14}H_{12}O_2NCl$ requires C, 64·2; H, 4·6%).

α-(5-Chloro-2-aminophenyl)-α-(4'-hydroxyphenyl)ethylene (V; $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = Cl$).—5-Chloro-2-amino-4'-hydroxybenzophenone was recovered unchanged after treatment with 3—4 equivalents of methylmagnesium iodide. Accordingly a solution of the ketone (10 g.) in ether (300 c.c.) was added to a Grignard solution prepared from magnesium (6·5 g.; 6·5 equivs.) and methyl iodide (40 g.) in ether (200 c.c.). A bright orange solid rapidly separated and methane was evolved. After 10 minutes, the solution was refluxed for 5 hours; it was then decomposed with ice and dilute hydrochloric acid, and the ethereal layer was washed,

dried, and evaporated. A solution of the residue in aqueous methanol deposited the *diaryl-ethylene* in faintly yellow cubes, which after several recrystallisations had m. p. 159°; yield, 6·7 g. (Found: C, 68·2; H, 4·8. $C_{14}H_{12}ONCl$ requires C, 68·4; H, 4·9%). It was recovered unchanged after being refluxed with sulphuric acid of various concentrations up to 8N.

The *dibenzoyl* derivative, prepared with benzoyl chloride and pyridine, was somewhat sparingly soluble in methanol; it separated from this solvent in clusters of colourless prisms, and from aqueous acetone in very slender, prismatic needles, m. p. 130·5—132° in each case (Found: C, 73·9; H, 4·3. $C_{28}H_{20}O_3NCl$ requires C, 74·0; H, 4·45%).

6-*Chloro*-4-(4′-*hydroxyphenyl*)*cinnoline*.—The suspension obtained by cooling a solution of the above aminoethylene (1 g.) in warm 2N-hydrochloric acid (60 c.c.) was treated at 5° with sodium nitrite (0·25 g. in 10 c.c. of water). After 1 hour, the precipitate was collected and dissolved in alcohol by the addition of ammonia, and the hot solution acidified with glacial acetic acid. The *cinnoline*, which separated on cooling, crystallised from slightly aqueous acetic acid in lustrous yellow plates with a red reflex, m. p. 257—259° (decomp.) (Found: C, 65·3; H, 3·5. $C_{14}H_9ON_2Cl$ requires C, 65·5; H, 3·5%).

The *benzoate*, prepared by the usual method, crystallised from aqueous alcohol in small, pale yellow needles, m. p. 156° (Found: C, 69·8; H, 3·8; N, 7·8; Cl, 9·6. $C_{21}H_{13}O_2N_2Cl$ requires C, 69·9; H, 3·6; N, 7·8; Cl, 9·85%).

5-*Chloro*-2-*amino*-2′-*hydroxy*-5′-*methylbenzophenone* (VII; $R_1 = OH$, $R_2 = H$, $R_3 = Me$, $R_4 = NH_2$).—The anthroxan prepared from *p*-cresol and *o*-nitrobenzaldehyde melted at 208—209° (Zincke and Siebert, *loc. cit.*, give m. p. 210°). On reduction with iron and acetic acid under the conditions already described for the anthroxan, m. p. 240°, a 65% yield of the pure amino-ketone was obtained; this formed small dull yellow needles, m. p. 114—115°, from acetic acid (Zincke and Siebert give m. p. 115°). The sparingly soluble *dibenzoyl* derivative separated from benzene–alcohol in small stout needles, m. p. 156—157° (Found: C, 71·5; H, 4·4. $C_{28}H_{20}O_4NCl$ requires C, 71·5; H, 4·3%). This derivative (380 mg.) was refluxed for 2 hours with 6 c.c. of 5% alcoholic potassium hydroxide, and the solution then concentrated, diluted with water, and made slightly acid with acetic acid; two crystallisations of the product from aqueous acetic acid gave the ketone, m. p. and mixed m. p. 114°.

2 : 5-*Dichloro*-2′-*hydroxy*-5′-*methylbenzophenone* (VII; $R_1 = OH$, $R_2 = H$, $R_3 = Me$, $R_4 = Cl$).—The foregoing amino-ketone (3 g.) was dissolved in warm glacial acetic acid (40 c.c.) and concentrated hydrochloric acid (5 c.c.) and cooled to 5—10°, and the suspension diazotised with sodium nitrite (1 g. in 50 c.c. of water). The solution, containing an appreciable flocculent precipitate, was added during 10 minutes to a hot solution of cuprous chloride (6 g.) in concentrated hydrochloric acid (60 c.c.) and water (50 c.c.); the suspension was then boiled for a few minutes and cooled. The product, crystallised twice from alcohol (charcoal), yielded the *dichloro-compound* in long yellow needles (2 g.), m. p. 149—150°, insoluble in aqueous sodium carbonate and only moderately soluble in hot alcohol (Found: C, 60·1; H, 3·6; Cl, 24·8. $C_{14}H_{10}O_2Cl_2$ requires C, 59·75; H, 3·6; Cl, 25·25%).

A suspension of the dichloro-phenol in aqueous sodium carbonate was oxidised by essentially the same procedure as that described for the oxidation of 2 : 5-dichloro-4′-hydroxybenzophenone. The resultant 2 : 5-dichlorobenzoic acid (250 mg. from 1 g. of the phenol) had m. p. and mixed m. p. 153—154°, and the identification was confirmed by its conversion into the *m*-nitroanilide, m. p. and mixed m. p. 151—152°. (When freshly prepared, the *m*-nitroanilide frequently shows a double melting point, melting at 138—139° to a vitreous mass which on further heating becomes opaque and then melts sharply at 151—152°.)

5-*Chloro*-2-*amino*-2′-*methoxy*-5′-*methylbenzophenone* (VII; $R_1 = OMe$, $R_2 = H$, $R_3 = Me$, $R_4 = NH_2$).—The anthroxan (2 g.), m. p. 208—209°, was added to a solution of sodium (0·2 g.) in methanol (35 c.c.) and refluxed with methyl iodide (3 c.c.) for 1½ hours. After dilution with water the crystalline precipitate obtained on scratching was twice recrystallised from aqueous methanol, the *methoxy-anthroxan* forming elongated yellow laminæ, m. p. 96—98°; more was obtained from the mother-liquors after removal of unmethylated anthroxan with dilute sodium hydroxide solution; total yield, 75% (Found: C, 65·6; H, 4·1; Cl, 12·7. $C_{15}H_{12}O_2NCl$ requires C, 65·8; H, 4·4; Cl, 13·0%).

A solution of the methoxy-anthroxan (1·25 g.) in glacial acetic acid (12·5 c.c.) was heated on the water-bath with iron filings (2 g.), added during 1½ hours; water (4 c.c.) was added after the reduction had been in progress for 10 minutes. After 1¾ hours the solution was largely diluted with water and extracted with ether. The filtered extract was washed with sodium carbonate solution and water, dried, and evaporated. A solution of the residue in aqueous methanol yielded the *amino-ketone* in small, dull yellow prisms; m. p. 100—101°, strongly depressed by the parent anthroxan (Found: C, 65·5; H, 5·1. $C_{15}H_{14}O_2NCl$ requires C, 65·3; H, 5·1%).

The ketone did not form a semicarbazone under the ordinary conditions, but yielded an N-*acetyl* derivative, which separated from aqueous methyl alcohol in cream-coloured, brittle, prismatic needles, m. p. 136—137° (Found: C, 64·7; H, 5·2. $C_{17}H_{16}O_3NCl$ requires C, 64·2; H, 5·1%).

α-(5-*Chloro*-2-*aminophenyl*)-α-(2′-*hydroxy*-5′-*methylphenyl*)*ethylene and Derivatives*.—A solution of 5-chloro-2-amino-2′-hydroxy-5′-methylbenzophenone (12 g.) in ether (400 c.c.) was refluxed with an ethereal solution of methylmagnesium iodide (from 7·2 g. of magnesium and 45 g. of methyl iodide) for 5 hours. The product was worked up in the usual way, yielding a brown viscous residue (13 g.). Portions of this material were treated as follows:

(i) When the resin was heated with its own weight of pyridine and of benzoyl chloride at 100° for 3 hours, it was converted into a crystalline *dibenzoyl* derivative, which separated from methanol in colourless prisms, m. p. 119° (Found: C, 74·4; H, 4·85. $C_{29}H_{22}O_3NCl$ requires C, 74·4; H, 4·75%). The dibenzoyl derivative (9·5 g.) was refluxed for 2 hours with potassium hydroxide (5·5 g.) in water (20 c.c.) and alcohol (40 c.c.), the solution concentrated, and water added. A solution of the copious white precipitate (presumably potassium salt) produced in hot alcohol was neutralised with sulphuric acid, diluted with water, and extracted with ether, furnishing a clear brown resin. A part of this (1·28 g.) on treatment with pyridine (2 c.c.) and benzoyl chloride (1·3 c.c.) at 100° gave a *compound* which was not identical with the original dibenzoyl derivative; it was very sparingly soluble in ether and in methyl and ethyl alcohols, and separated from benzene–alcohol in fine colourless needles, m. p. 235° (Found: C, 75·45; H, 4·67; N, 2·4; Cl, 6·55. $C_{36}H_{26}O_4NCl$ requires C, 75·6; H, 4·6; N, 2·45; Cl, 6·2%).

(ii) A solution of the crude resin in hot methanol was filtered (charcoal) and warmed with dilute hydrochloric acid. On cooling, pale yellow prismatic needles of the *hydrochloride* separated. This, dissolved in aqueous methanol and reprecipitated with concentrated hydrochloric acid, formed pale yellow prisms, m. p. 222—223° (decomp.) (Found: Cl, 23·5. $C_{15}H_{14}ONCl$, HCl requires Cl, 24·0%).

The base was obtained from the hydrochloride by addition of a slight excess of ammonia to its solution in aqueous methanol. After being warmed on the water-bath for 10 minutes, the solution was cooled and extracted with ether. Concentration of the dried extract to a small volume and addition of ligroin (b. p. 40—60°) precipitated some resin, followed by crystalline material. The latter was repeatedly crystallised from ether–ligroin, from which the *diarylethylene* separated in clusters of cream-coloured prismatic needles, m. p. 108° (yield, *ca.* 50%) (Found: C, 69·05; H, 5·4. $C_{15}H_{14}ONCl$ requires C, 69·3; H, 5·4%).

6-Chloro-4-(2′-hydroxy-5′-methylphenyl)cinnoline.—A suspension of the above hydrochloride (2·5 g.) in dilute hydrochloric acid (150 c.c.) was cooled to 0°, and a solution of sodium nitrite (0·63 g.) in water (10 c.c.) added slowly with mechanical stirring. The precipitate was collected after 1 hour and purified exactly as described for 6-chloro-4-(4′-hydroxyphenyl)cinnoline. The pure *cinnoline* formed small, golden, prismatic needles (0·9 g.), m. p. 260—261° (decomp.) (Found: C, 66·7; H, 4·2; N, 10·2. $C_{15}H_{11}ON_2Cl$ requires C, 66·5; H, 4·1; N, 10·35%). The compound was also obtained by the action of hydrochloric acid and sodium nitrite on the crude resinous diaryl-ethylene. Like the analogue already described, this hydroxy-cinnoline is very sparingly soluble in both cold and hot alcohol, benzene, and ethyl acetate.

Treatment of the cinnoline (0·4 g.) with benzoyl chloride (0·25 g.) and pyridine (1 c.c.) at 100° for 2 hours produced some decomposition and gave only a poor yield (30%) of the *benzoate*; this was very soluble in methyl alcohol, and formed yellow prisms, m. p. 140°, from ether–ligroin (Found: C, 69·9; H, 4·0. $C_{22}H_{15}O_2N_2Cl$ requires C, 70·5; H, 4·0%).

Grateful acknowledgment is made to the Chemical Society for a grant.

DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. [*Received, December 22nd*, 1941.]

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59. *The Magnitude of the Solvent Effect in Dipole-moment Measurements. Part V. The Solvent-effect Constant and the Moments of Alkyl Iodides.*

By ARNOLD AUDSLEY and FRANK R. GOSS.

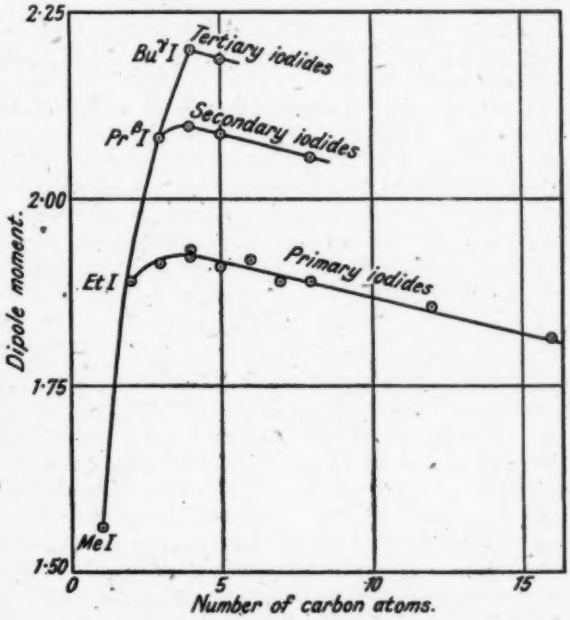
The dielectric polarisation of binary mixtures of eighteen alkyl iodides with carbon tetrachloride has been shown to obey the solvent-effect equation introduced in Part I (J., 1937, 1915). The dipole moments of these iodides have been calculated from the coefficients in this equation by means of the intercept ratio (Part II, J., 1940, 752) and by making use of the additive character of the atom polarisation postulated in Part IV (J., 1941, 864), for which further evidence is now given. The solvent-effect constant [*K*] is defined, and its relationship to molecular structure summarised. The function of the solvent-effect equation and constant is shown to be that of adapting dipole formulæ based on the Lorenz field to the more correct model proposed by Onsager. The moments and the solvent-effect constants of the alkyl iodides fall into regular series, primary, secondary, and tertiary, the primary being modified by an alternation of the odd and even members. The moments in each series exhibit a decrement of 0·01 D. for each member of the series, this being modified by systematic differences attributable in the case of the lowest members to induced moments. It is deduced that alkyl chains in the liquid phase are curled, whereas in the vapour phase they are free to rotate. In the series Me, Et, Pr^{β}, Bu^{γ} the induced moments can be calculated from a group dipole moment of 0·64 for the methyl group. The calculated atom polarisations increase very slightly with increasing chain length, being, as explained in Part IV, mainly dependent on the nature of the polar atom.

Dipole Moments of the Alkyl Iodides.—In Part IV (*loc. cit.*) it has been shown that by combining polarisation data in both the liquid and the vapour state, the dipole moments of an entire homologous series may be derived reasonably free from any uncertainty due to the difficulties in the way of direct

measurement of P_{E+A}. This procedure can be applied with special confidence to the alkyl iodides, since both methyl and ethyl iodide have been found (*loc. cit.*) to give the same contributory value of P_{E+A} for the iodine atom. A number of the higher alkyl iodides have now been examined in the liquid state, and the results are summarised in Fig. 1 and Table I. Solvent-effect corrections have been applied in a uniform manner throughout the series in accordance with principles elaborated in earlier papers. Additive values of P_{E+A} (see below) have been calculated from the contributory values given in Table II of Part IV with addition of the appropriate enhancements for the branched-chain members, corresponding to experimental measurements for the molecular refractivity.

FIG. 1.

Dipole moments of alkyl iodides.



The moments vary from a minimum value for methyl iodide to a maximum at *tert.*-butyl iodide. Increasing complexity of the hydrocarbon residue involves reinforcement of the primary moment of the C–I bond by vectorial components of the induced moments in the adjacent C–C bonds up to the butyl compounds. The increases in these moments due to the successive replacement of the three hydrogens of methyl iodide by methyl groups for Et, Pr$^{\beta}$, and Bu$^{\gamma}$ are seen to be 0·33, 0·52, and 0·64, respectively. The magnitude of these increases can be accounted for by the assumption that the induced moment in each bond is 0·64, and the angle between them tetrahedral.

Evidence concerning the increase in moment with lengthening of the alkyl chain, and the possibility that a constant value might be reached at some point in the series, has been summarised by Cowley and Partington (J., 1938, 977). Measurements have now been extended as far as cetyl iodide. Up to the butyl members there is a small series induced moment, but beyond this point there is a regular decrement of 0·01 D., not only in the primary, but also in the secondary and tertiary series. This must be due to a reversal in direction of the component of the induced moment, owing to the flexible nature of the chain. This reversed induced moment is more pronounced in alkyl chlorides and bromides and is recognisable right from the *n*-propyl derivatives, and it has been noted by Stuart (*Physikal. Z.*, 1930, **31**, 80) in the case of *n*-propyl chloride. He showed that the induced moment may fall outside that space within which the primary moment should be reinforced by the induced moments. Likewise, Cowley and Partington

TABLE I.

Polarisation constants of carbon tetrachloride solutions at 20°.

	Calc. values.*			Exptl. values,	Derived poln. coefficients.			Solvent-effect constant,	Corrected dipole moment,
	P_{E+A}.	P_E.	P_A.	P_∞.	Z.	Y.	P_O.	$[K]$.	μ, D.
Methyl iodide	21·9	18·5	3·4	63·3	34·3	92·1	51·2	1·72	1·56
Ethyl iodide	26·7	23·3	3·4	89·9	47·3	140·5	75·1	1·62	1·89
n-Propyl iodide	31·3	27·9	3·4	98·7	61·7	149·9	77·3	1·53	1·92
*iso*Propyl iodide	31·7	28·3	3·4	113·0	67·1	180·8	91·0	1·47	2·08
n-Butyl iodide	35·8	32·4	3·4	105·6	74·6	154·9	78·4	1·49	1·93
*iso*Butyl iodide	35·8	32·4	3·4	107·0	80·0	157·7	78·0	1·43	1·92
sec.-Butyl iodide	36·2	32·8	3·4	121·9	84·5	190·2	92·6	1·39	2·10
tert.-Butyl iodide	36·9	33·5	3·4	132·0	88·8	211·1	101·7	1·36	2·20
n-Amyl iodide	40·3	36·9	3·4	111·2	92·9	157·0	76·8	1·40	1·91
β-Iodopentane	40·6	37·2	3·4	128·4	104·0	194·5	91·7	1·30	2·09
γ-Iodopentane	40·5	37·1	3·4	128·3	104·5	194·8	91·6	1·30	2·09
tert.-Amyl iodide	41·0	37·6	3·4	137·7	106·5	214·5	100·6	1·29	2·19
n-Hexyl iodide	44·9	41·4	3·5	117·0	105·7	159·6	77·5	1·38	1·92
n-Heptyl iodide	49·4	46·9	3·5	120·0	119·6	156·1	75·1	1·36	1·89
n-Octyl iodide	53·9	51·4	3·5	124·7	131·1	156·4	75·1	1·35	1·89
β-Iodo-octane	54·1	51·6	3·5	144·0	160·0	198·3	88·9	1·16	2·06
Lauryl iodide	72·0	69·5	3·5	142·7	182·7	152·9	72·3	1·31	1·85
Cetyl iodide	90·2	87·6	3·6	158·5	240·5	148·9	69·2	1·26	1·81

* Calculated from the contributory values recorded in J., 1941, 864, Table II.

(*loc. cit.*, p. 979) deduced that, although the bulk of the polarisable matter added by lengthening the hydrocarbon chain of compounds with a negative solvent effect (solvent-effect constant, $[K]>1$, see below) augments the primary moment, yet parts of the molecule may occupy positions leading to a diminution of the moment. This prediction has thus been realised for the higher alkyl iodides. However, as the above authors and also Frank (*Proc. Roy. Soc.*, 1935, *A*, **152**, 171) point out, the approximations made in the theoretical derivation of the sign and magnitude of the induced moments to not permit of rigid and exact calculation.

In the primary series of iodides there is an alternation, the even members having higher and the odd ones lower moments than the average. After allowance for an experimental error of $\pm 0{\cdot}01$ D., this deviation of the odd and even members has the value of 0·01 D. The moment for *iso*butyl iodide falls on the curve of the odd members, and is nearly identical with that for *n*-propyl iodide which has the same chain length. The moments of the two secondary amyl iodides lie on the secondary curve and are identical. These moments, recorded in Table I, depend on the use of the additive values of P_{E+A} given in Part IV, and do not differ by more than 0·03 D. from those calculated from the empirical relationship $P_{E+A} = 1{\cdot}05\ [R_L]_D$. Hence, our conclusions regarding the influence of the alkyl radicals on the moments are independent of any assumption concerning the magnitude of P_{E+A}. However, we provide further evidence (see p. 363) in favour of the additive method of assessing P_{E+A}.

Definition of the Solvent-effect Constant.—The solvent-effect constant, $[K]$, expresses the effect of the field anistropy on the polarisation. The method of deriving $[K]$ has been described in Part II (J., 1940, 754) where the symbol K was used. The scale of $[K]$ was devised in such a way that it has a natural *fixed point* of unity for symmetrical molecules, but has an arbitrary *unit* chosen to give values for the reference compounds (see Table II) most nearly corresponding with those of the ratio of their respective optical polarisation axes $2b_1/(b_2 + b_3)$ as calculated by Higasi (*Sci. Papers Inst. Phys. Chem. Res. Tokyo*, 1936, **28**, 284). It follows from its derivation from the coefficients Y and Z of the solvent-effect equation (see below), by the expressions given below, that for a very long molecule, for which Z might conceivably approach very closely to zero and hence have Y equal to P_O, $[K]$ would have the value 2·73. This value appears therefore to form an upper limit to the scale of solvent-effect constants. As the ratio of the molecular axes could, at least in theory, extend to infinity, the equivalence between $[K]$ and $2b_1/(b_2 + b_3)$ is seen to be only a *first approximation*, as was stated in Part II.

It was explained in Part I that the solvent effect can be expressed by the equation for the partial polarisation of either component of a binary liquid mixture, $P_S = P_{E+A} + Z(\varepsilon - 1)^4/(\varepsilon + 2)^4 + Y/\varepsilon$, where the Y/ε term expresses the change in the orientation polarisation (P_O) due to the induced moments

TABLE II.

Equivalence of certain solvent-effect constants with the corresponding ratios of the optical polarisation axes.

	$[K]$.	$2b_1/(b_2 + b_3)$.		$[K]$.	$2b_1/(b_2 + b_3)$.
Nitrobenzene	1·68	1·69	Acetone	1·15	1·19
Chlorobenzene	1·61	1·53	Chloroform	0·70	0·74

arising from the neighbouring dipoles (this may be a diminution or augmentation according to the shape of the molecules), whilst $Z(\varepsilon - 1)^4/(\varepsilon + 2)^4$ is the enhancement by these dipoles of the distortion polarisation (P_{E+A}). These induced moments depend in magnitude and direction on modifications of the local field due to interaction of molecules in the liquid state, the Y and Z components of the solvent effect being dependent on the field anisotropy caused by the dissymmetry of the polar molecules. *The solvent-effect constant* $[K]$ is, as argued in Part II, *a measure of the shape of the molecule*, since *it expresses the proportion of the polarisable matter which is disposed along the dipole axis*; it consequently bears a constant relation to both the Y and the Z component of the solvent effect, so that if $[K]$ is known, the solvent effect for the carbon tetrachloride mixture can be immediately calculated. The relationship between $[K]$, Y, and Z is defined in the manner already described, in such a way that for symmetrical molecules $[K]$ is unity. As deduced in Part II, $[K] = 4 - 2{\cdot}85Y/\varepsilon_1 P_O = 6{\cdot}55 - 3{\cdot}82\sqrt[4]{(Z + P_{E+A})/P_{E+A}}$ (where ε_1 is the dielectric constant of the solvent). Hence we may derive the intercept ratio $(Y/P_O - 1)/[\sqrt[4]{(Z + P_{E+A})/P_{E+A}} - 1] = 3$*, which has been extensively employed in this work to calculate P_O from the intercepts Y and Z. The ratio $Y/\varepsilon_1 P_O$ is usually less or greater than unity (see Part I) according as the partial polarisation of the infinitely dilute solution (P_∞) is less than or greater than the polarisation of the vapour, or again, according as the moment lies along the major or one of the minor axes of the molecule, or as the Kerr constant is positive or negative, in accordance with the generalisation of Higasi (*loc. cit.*; cf. *Bull. Inst. Phys. Chem. Res. Tokyo*, 1934, **13**, 1167; 1935, **14**, 146); *i.e.*, as $[K]$ is greater or less than unity.

* The value 3·25 assigned to this ratio in Part I was corrected to 3 in Part II.

If Higasi's generalisation were strictly true, $Y/\varepsilon_1 P_0$ should be *exactly* unity for any symmetrical molecule, because $P_\infty - P_{E+A}$, which approximates to Y/ε_1 would equal P_0; $[K]$, being unity, would then have the values $4 - 3Y/\varepsilon_1 P_0$ or $4 + 6/\varepsilon_1 - 9\sqrt[3]{(Z + P_{E+A})/P_{E+A}}/\varepsilon_1$. However, Frank has pointed out (*loc. cit.*, p. 180) that in the theoretical treatment of the solvent effect "the field distribution is considered to be always the same as it is in a uniform medium." In the binary liquid mixtures now under consideration the distribution necessarily varies, and consequently "the chief result of this error is that the molecules considered to have zero solvent effect according to the simple deduction, will actually show a positive effect." This error is compensated for in our derivation of the solvent-effect constant by the addition of an empirical term $0{\cdot}15Y/\varepsilon_1 P_0$, which, together with the value $4 - 3Y/\varepsilon_1 P_0$ obtained by applying the Higasi generalisation, gives finally the above correct expression for $[K]$, *viz.*, $4 - 2{\cdot}85Y/\varepsilon_1 P_0$ as first obtained in Part II of this series.

Interpretation of the Solvent Effects in Terms of the Solvent-effect Constant and the Onsager Field.—The use of the solvent-effect constant enables us to adapt the Debye theory to the liquid state even when the molecular shapes are far from spherical. Onsager (*J. Amer. Chem. Soc.*, 1936, **58**, 1486; see also Cole, *J. Chem. Physics*, 1938, **6**, 385, and Kirkwood, *ibid.*, 1939, **7**, 911), on the contrary, has rejected the Debye formula as applied to liquids and has proposed an expression for the dipole moment of liquid molecules which, as he admits, is open to the objections that the molecules are assumed to be spherical, and also to fill the whole volume of the liquid. His formula is somewhat complex for actual application to the measurement of dipole moments and, as he says, requires "some arbitrary exercise of judgement." Onsager's equation, as it applies to homogeneous liquids, has been employed by Böttcher (*Physica*, 1939, **6**, 59), who found quite good agreement in certain cases. An examination of his figures shows, however, that the discrepancies are most marked where the molecules are farthest removed from the spherical shape assumed by Onsager. Those having $[K]>1$ have low values of the moment in Böttcher's tabulation and *vice versa*, just as in the Debye theory. The Onsager formula for binary mixtures is more complicated, but it has been applied by Rodebush and Eddy (*J. Chem. Physics*, 1940, **8**, 424; see also Hobbs, *ibid.*, 1939, **7**, 849, and Piekara, *Proc. Roy. Soc.*, 1939, *A*, **172**, 360), who obtain values which are in general also too low or too high according as $[K]$ is $>$ or <1. Van Vleck (*J. Chem. Physics*, 1937, **5**, 556) discussed the Lorenz and the Onsager model of the local field, which have been depicted by Falkenhagen (*Physikal. Z.*, 1938, **39**, 806; cf. van Vleck, *J. Chem. Physics*, 1937, **5**, 320) (see Fig. 2). Van Vleck pointed out that "there is apparently no easy way to decide by simple physical considerations" which "is really the better." From work in this series, it has been concluded (see Part II) that the Onsager field model is the more correct, but that, since the shape of the molecule also affects the field distribution, the empirical solvent-effect equation gives a truer expression for the polarisation than Onsager's complex dipole formula, for which he assumes a spherical molecule. In the solvent-effect equation, $P_S = P_{E+A} + Z(\varepsilon - 1)^4/(\varepsilon + 2)^4 + Y/\varepsilon$, the Onsager reaction field R, shown in Fig. 2 by broken lines, corresponds to the $Z(\varepsilon - 1)^4/(\varepsilon + 2)^4$ term, which is an enhancement of the polarisation, and is independent of the moment because the field R is parallel to the dipole. The cavity field G (continuous lines) similarly corresponds to $P_{E+A} + Y/\varepsilon$, which expresses the difference between the classical polarisation $P_{E+A} + P_O$, arising from the internal field, and the opposing effect of the induced moments due to G. Onsager has criticised the Debye formula because highly polar compounds do not exhibit a Curie point or a permanent electric polarisation, involving an apparent volume polarisation greater than unity. However, the Lorenz field being assumed, the local polarisation of a single liquid molecule will be given by $(\varepsilon - 1)/(\varepsilon + 2) = P^{vap}.d/M$, which in the case of nitrobenzene has a value of 4·3, thus fulfilling Onsager's requirement. In the Onsager field this value is reduced by the effects of the surrounding molecules to the average volume polarisation of 0·9 actually observed.

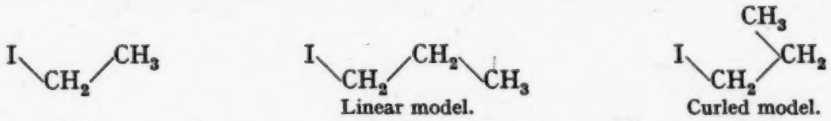
FIG. 2.

Lorenz field. *Onsager field.*

Rodebush and Eddy (*loc. cit.*) regard the polarisation of benzene–ethyl ether mixtures as providing special evidence against the Debye theory. They assume with Debye ("Polar Molecules," 1929, p. 46) that, for this mixture, the partial polarisation of the ether is independent of concentration. There is, however, nothing remarkable about this particular mixture and any difference from the usual curves is a difference of degree and not of kind. It just happens that $[K]$ for diethyl ether has the small value of 0·22, and consequently the polarisation of the pure liquid ether is only slightly less than that of the molecules in dilute solution. For carbon tetrachloride–ethyl ether mixtures, the difference is a little greater (see Part I), and indeed, there is nothing unusual about these mixtures to provide any evidence for or against any particular theory. Rodebush and Eddy have a further criticism of the Debye method

of extrapolating polarisation data in dilute solutions to obtain P_∞; this criticism is met in our work by the employment of the tangent method of obtaining the partial polarisations. The same value of P_∞ is obtained in either case, and in practice we use both methods to ensure the greatest possible accuracy.

Solvent-effect Constants and Structure of the Alkyl Iodides.—All the alkyl iodides dealt with in this paper have a solvent-effect constant greater than unity (see Fig. 3 and Table I). In the series Me, Et, Pr^β, Bu^γ there is a regular fall for each member. This is accompanied by alternation of the odd and even members. The constant decreases at first rapidly, but beyond the fifth member more slowly with increasing chain length. This is in agreement with our interpretation of the series decrement of the dipole moments (see above). It appears that in the liquid state the alkyl chains must be curled in the manner proposed by Stuart (*loc. cit.*). A propyl iodide molecule of linear structure (II) has, by comparison with

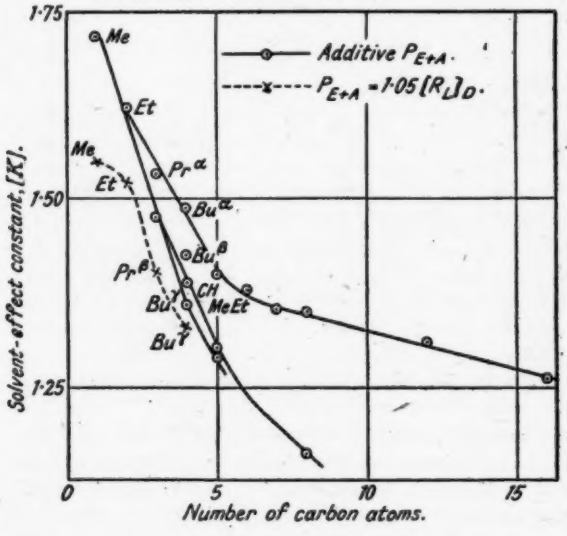


(I.) (II.) (III.)

ethyl iodide (I), had its length extended in line with the dipole, and should have a larger $[K]$ than its lower homologue. The experimentally observed lowering of $[K]$ is in agreement with Stuart's curled structure (III). Therefore the experimental evidence of both dipole moments and solvent-effect constants is in favour of this curled form for the liquid molecules, although the amount of curl is not sufficient to affect the moment until beyond butyl iodide. The effect of this curling on the shape of the molecule should be most marked for the first five members of a series, after which a pseudo-ring will have been formed. This will be seen from Fig. 3 to be in agreement with the ascertained facts. After the fifth member, although $[K]$ continues to fall, with presumably further curling of the chain, the effect on the shape of the molecule is greatly diminished. The value of $[K]$ shows a marked alternation in the primary series, which, owing to the known relationships between the solvent-effect constant on the one hand and melting points on the other with molecular symmetry, may be compared with the alternation of the melting points of the primary series of alkyl halides (Baker and Smyth, *J. Amer. Chem. Soc.*, 1939, **61**, 1695).

FIG. 3.

Solvent-effect constants of alkyl iodides.



The change in solvent effect with increasing length of the alkyl chains is in a direction contrary to that expected by Frank (*loc. cit.*, p. 187). Consequently, the relative differences of the change of radical and solvent effect do not explain, as was supposed by Cowley and Partington (*loc. cit.*, p. 981), the fact that the moments of *n*-propyl and *n*-butyl iodides have higher values in the vapour than in the liquid state. This difference appears to persist even after correction for solvent effect and for atom polarisation, and is recorded in Table III, where the moments obtained in the present work from measurements in the liquid

TABLE III.

Comparison of dipole moments measured in the liquid and the vapour phase.

		Dipole moments.		
		Liquid phase, corrected for solvent effect.	Vapour phase.	
	P_{E+A}.		Smyth and McAlpine.	Groves and Sugden.
Methyl iodide	21·9	1·56	1·56	1·62
Ethyl iodide	26·7	1·89	1·89	1·86
n-Propyl iodide	31·3	1·92	—	2·00
n-Butyl iodide	35·8	1·93	—	2·07

phase are compared with vapour values. The latter have been recalculated, the additive values of P_{E+A} given in Table I being used. Agreement of the present values for methyl and ethyl iodides with those of Smyth and McAlpine (*J. Chem. Physics*, 1934, **2**, 499) is a necessary consequence of the use of their

measurements (which were corrected by them for ideal-gas deviations) to calculate the value of P_{E+A} for the iodine atom (see Part IV). In considering this divergence between the vapour values of Groves and Sugden (J., 1937, 158) and our corrected values for the liquid phase, which is restricted to those iodides with chains of two or more carbon atoms, it is evident that, although we have shown that in the liquid state these molecules have a curled structure (III), yet the alkyl chains in the vapour molecules may well have greater freedom of rotation, with the consequence that the statistical average may be somewhere between the curled and the linear forms (II and III). This would result in a higher moment, so that our hypothesis affords a complete explanation of the available data.

TABLE IV.

Criteria of purity.

	Observed values.		Previously recorded.			Observed values.		Previously recorded.	
Iodide.	$d_4^{20°}$.	$n_D^{20°}$.	$d_4^{20°}$.	$n_D^{20°}$.	Iodide.	$d_4^{20°}$.	$n_D^{20°}$.	$d_4^{20°}$.	$n_D^{20°}$.
n-Propyl	1·7458	1·5050	1·7471 [2]	1·5051 [1]	γ-Iodopentane	1·5128	1·4979	1·5176 [4]	1·4968 [4]
*iso*Propyl	1·7043	1·4991	1·7042 [3]	1·4997 [1]	*tert.*-Amyl	1·4937	1·4981	—	—
n-Butyl	1·6137	1·5000	1·6123 [2]	1·5001 [1]	*n*-Hexyl	1·4329	1·4930	1·4387 [2]	1·4929 [2]
*iso*Butyl	1·6038	1·4961	1·6035 [3]	1·4960 [1]	*n*-Heptyl	1·3792	1·4909	1·3790 [5]	1·4905 [5]
sec.-Butyl	1·5984	1·5000	1·5975 [3]	1·5001 [3]	*n*-Octyl	1·3295	1·4890	1·3299 [5]	1·4886 [5]
tert.-Butyl	1·5445	1·4918	—	—	β-Iodo-octane...	1·3251	1·4896	—	—
n-Amyl	1·5108	1·4965	1·5095 [3]	1·4955 [3]	Lauryl	1·2015	1·4844	—	—
β-Iodopentane...	1·5020	1·4960	—	—	Cetyl	1·1207 [7]	1·4817 [7]	1·1264 [6]	1·4826 [6]

[1] Brühl, *Annalen*, 1880, **203**, 1. [2] Karvonen, *Ann. Acad. Sci. Fennicæ*, 1914, *A*, **5**, 1. [3] Timmermans and Delcourt, *J. Chim. physique*, 1934, **31**, 85. [4] Rosanoff, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 180. [5] Deffet, *Bull. Soc. chim. Belg.*, 1931, **40**, 385. [6] Delcourt, *ibid.*, p. 284 (extrapolated values). [7] Supercooled liquid.

The experimental polarisation data for methyl and ethyl iodide have been recorded in Part IV. The coefficients for the higher iodides have been calculated from the data in Table V, use being made of the additive character of P_{E+A} postulated in Part IV, of the solvent-effect equation, and of the intercept ratio. These general empirical equations, previously developed for the solvent effect, are now further confirmed. The number of polar compounds already examined has been doubled, and it is found that amongst all 36 compounds of widely differing chemical type, the partial-polarisation data fit the solvent-effect equations as shown in Fig. 4, and the constants Y, Z, $[K]$, and μ are independent of the concentration of the binary mixtures. Similarly, the partial polarisations of the carbon tetrachloride in all the mixtures depend on the dielectric constants of the mixtures and are largely independent of the other component of the mixture. As explained in earlier papers, the partial polarisations only become to some extent dependent on the nature of the polar components when, owing to anisotropy effects, the polar compounds have low values of the solvent-effect constant. This consideration does not apply to the alkyl iodides here investigated.

The solvent-effect constants of these alkyl iodides appear to provide further support for our view (Part IV) that a correct evaluation of P_{E+A} is given by additive values based on solvent-effect data and obtained by the elimination method. In Fig. 3 we have plotted, in addition to the values of $[K]$ from Table I, some of the corresponding figures which would be given on a basis of $P_{E+A} = 1{\cdot}05\,[R_L]_D$. The values do not show the regular fall for the series Me, Et, Pr^{β}, Bu^{γ} which is to be expected from the regular increase in symmetry. It will be seen that the value of P_{E+A} has a considerable influence on $[K]$, unlike its negligible effect on the moment, and it is for this reason that it is necessary to decide on the best way of determining P_{E+A}.

The extensive confirmation of the solvent-effect theory given in this paper is illustrated in Fig. 4, where the partial polarisations of some of the iodides and of carbon tetrachloride are plotted against $1/\varepsilon$, and the characteristic shape of the curves for both polar and non-polar compounds may be compared with others to be found in Parts I, II, and III of this series (*locc. cit.* and J., 1940, 888).

EXPERIMENTAL.

Density, dielectric constant, and temperature were measured as previously described (Goss, J., 1933, 1343; 1935, 730; 1940, 893).

Preparation and Purification of Materials.—(A) n- *and* iso-*Propyl and* n-*octyl iodides.* B.D.H. Samples were washed with sodium carbonate and thiosulphate solutions and with water, dried with calcium chloride, and distilled, the middle fraction being collected.

(B) *Cetyl iodide.* A B.D.H. sample was liquefied then washed and dried as in section (A). The middle fraction had b. p. 156°/0·5 mm., m. p. 225°. (The physical constants at 20° recorded in Tables III and IV for this substance apply to the supercooled liquid.)

(C) n- *and* iso-*Butyl*, n-*amyl, and lauryl iodides.* These were obtained from the middle fractions distilled

TABLE V.

Polarisations of carbon tetrachloride mixtures at 20°.

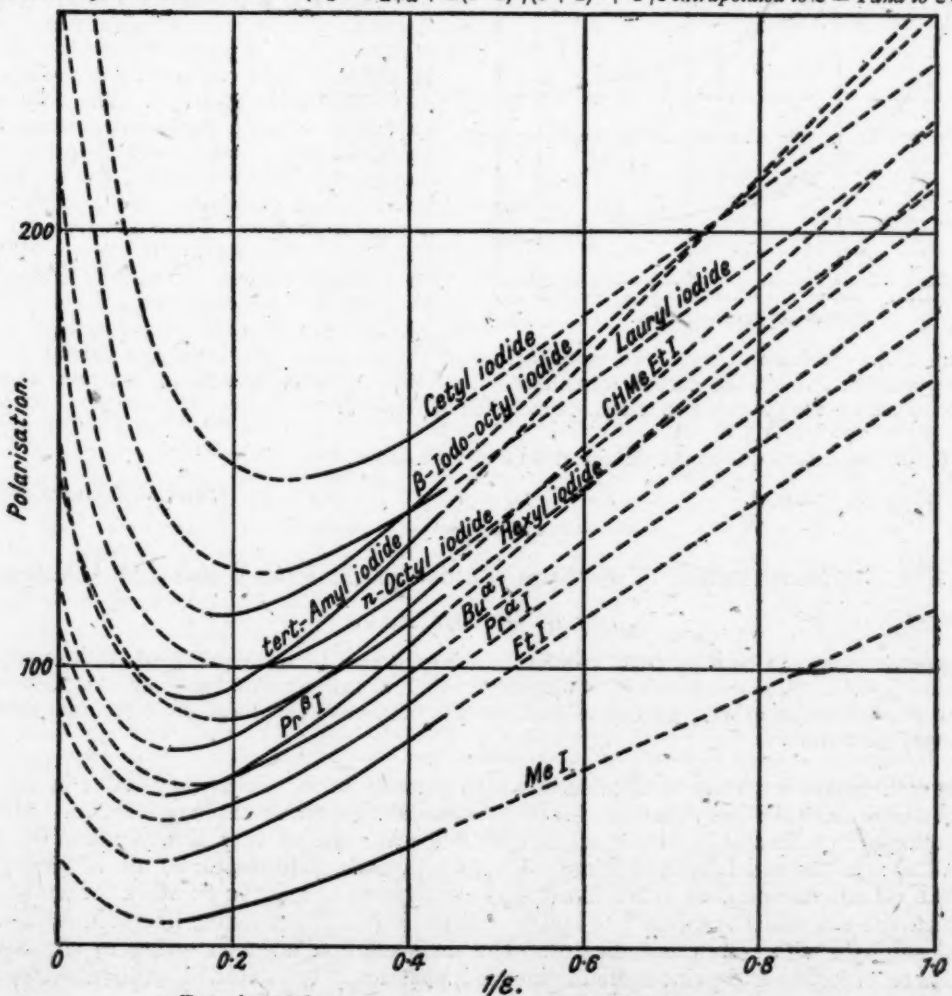
c_2.	ϵ.	$d_4^{20°}$.	P_{12}.	P_{S2}.	P_{S1}.	c_2.	ϵ.	$d_4^{20°}$.	P_{12}.	P_{S2}.	P_{S1}.
		n-*Propyl iodide.*						iso*Propyl iodide.*			
0·00000	2·2376	1·5937	28·19	99	28·2	0·00000	2·2353	1·5939	28·15	113	28·2
0·00559	2·2631	1·5946	28·60	98	28·2	0·00559	2·2662	1·5944	28·65	112	28·2
0·01185	2·2898	1·5956	29·02	97	28·2	0·01137	2·2976	1·5951	29·15	111	28·2
0·02384	2·3379	1·5980	29·76	96	28·3	0·02142	2·3494	1·5963	29·96	109	28·2
0·03347	2·3834	1·5989	30·47	95	28·3	0·04354	2·4644	1·5990	31·70	105	28·3
0·04504	2·4350	1·6008	31·24	93	28·3	0·06717	2·5804	1·6018	33·37	102	28·5
0·05154	2·4577	1·6023	31·56	93	28·3	0·09591	2·7318	1·6054	35·42	99	28·7
0·07652	2·5703	1·6067	33·16	90	28·5	0·23752	3·538	1·6224	44·54	86	32
0·12662	2·7999	1·6141	36·21	86	29	0·39262	4·464	1·6406	52·32	78	36
0·17142	3·0045	1·6210	38·70	83	30	0·65918	6·101	1·6702	62·01	72	43
0·24475	3·364	1·6327	42·59	78	31	0·85118	7·280	1·6898	67·12	71	46
0·48505	4·568	1·6703	52·58	70	36	1·00000	8·194	1·7043	70·39	70·4	49
0·74250	5·789	1·7088	59·67	66	41						
1·00000	7·004	1·7458	64·93	64·9	45						
		n-*Butyl iodide.*						iso*Butyl iodide.*			
0·00000	2·2365	1·5938	28·17	106	28·2	0·00000	2·2350	1·5934	28·15	107	28·2
0·00457	2·2571	1·5939	28·52	105	28·2	0·00677	2·2673	1·5935	28·71	106	28·2
0·00966	2·2792	1·5941	28·90	105	28·2	0·01236	2·2917	1·5936	29·12	105	28·2
0·01817	2·3178	1·5943	29·55	104	28·2	0·02562	2·3508	1·5937	30·12	103	28·3
0·03376	2·3881	1·5946	30·72	102	28·3	0·05858	2·5002	1·5943	32·54	99	28·4
0·06361	2·5251	1·5954	32·90	99	28·4	0·08669	2·6395	1·5946	34·67	96	28·6
0·12099	2·7804	1·5969	36·73	94	29	0·12355	2·7943	1·5952	36·96	92	29·0
0·23061	3·286	1·5996	43·47	86	30	0·28691	3·537	1·5976	46·60	83	32
0·44686	4·273	1·6043	54·42	77	35	0·63659	5·037	1·6016	61·99	75	38
0·73421	5·453	1·6088	65·36	73	40	1·00000	6·466	1·6038	74·08	74·1	44
1·00000	6·288	1·6137	72·76	72·8	43						
		sec.-*Butyl iodide.*						tert.-*Butyl iodide.*			
0·00000	2·2359	1·5937	28·16	122	28·2	0·00000	2·2351	1·5939	28·14	132	28·2
0·00923	2·2362	1·5938	29·02	120	28·2	0·00775	2·2846	1·5935	28·99	130	28·2
0·01321	2·3089	1·5939	29·39	119	28·2	0·01478	2·3241	1·5932	29·65	129	28·2
0·02777	2·3872	1·5940	30·68	117	28·3	0·02843	2·4051	1·5925	30·98	126	28·3
0·05126	2·5195	1·5943	32·77	113	28·4	0·05531	2·5736	1·5912	33·62	121	28·5
0·11572	2·8934	1·5952	38·16	106	29·2	0·10813	2·8983	1·5877	38·34	114	29
0·21257	3·448	1·5964	45·11	98	31	0·21238	3·582	1·5838	46·80	104	31
0·45961	4·904	1·5986	59·33	85	38	0·23846	3·756	1·5820	48·74	102	32
0·73044	6·439	1·5993	70·88	81	44	0·42229	4·935	1·5721	60·12	92	37
1·00000	7·874	1·5984	80·15	80·2	48	0·52197	5·619	1·5687	65·54	89	39
						0·67022	6·506	1·5613	72·17	86	43
						1·00000	8·416	1·5445	84·83	84·8	50
		n-*Amyl iodide.*						*β-Iodopentane.*			
0·00000	2·2374	1·5942	28·18	111	28·2	0·00000	2·2350	1·5940	28·14	144	28·1
0·00912	2·2774	1·5930	28·91	110	28·2	0·00488	2·2621	1·5916	28·70	143	28·2
0·01437	2·3015	1·5924	29·35	109	28·2	0·00888	2·2865	1·5896	29·19	142	28·2
0·02597	2·3533	1·5913	30·28	108	28·2	0·01775	2·3327	1·5853	30·14	140	28·2
0·04734	2·4514	1·5890	32·00	105	28·3	0·03742	2·4405	1·5759	32·33	137	28·3
0·10562	2·6948	1·5832	36·14	99	28·7	0·07249	2·6277	1·5599	36·10	132	28·5
0·24796	3·294	1·5695	45·50	90	31	0·16219	3·080	1·5227	45·13	126	30
0·64658	4·788	1·5364	66·26	82	37	0·34834	3·915	1·4601	62·07	118	32
1·00000	5·811	1·5108	80·74	80·7	42	0·67275	5·009	1·3811	87·75	112	37
						1·00000	5·770	1·3251	111·24	111·2	41
		γ-Iodopentane.						tert.-*Amyl iodide.*			
0·00000	2·2390	1·5943	28·20	128	28·2	0·00000	2·2350	1·5940	28·14	138	28·1
0·00597	2·2732	1·5936	28·81	127	28·2	0·00698	2·2781	1·5932	28·90	136	28·2
0·01137	2·3009	1·5931	29·30	126	28·2	0·01174	2·3070	1·5925	29·41	135	28·2
0·02078	2·3541	1·5922	30·23	125	28·3	0·02106	2·3644	1·5913	30·40	133	28·2
0·03821	2·4538	1·5903	31·92	122	28·3	0·03837	2·4722	1·5892	32·22	131	28·3
0·08002	2·6917	1·5862	35·77	117	28·7	0·07715	2·7174	1·5844	36·13	125	28·7
0·13920	3·032	1·5803	40·88	111	30	0·22309	3·668	1·5674	49·16	111	32
0·28936	3·915	1·5666	52·42	100	33	0·65807	6·386	1·5231	77·14	95	42
0·69252	6·055	1·5342	75·45	90	42	1·00000	8·192	1·4937	93·56	93·6	49
1·00000	7·432	1·5128	89·27	89·3	47						
		n-*Hexyl iodide.*						n-*Heptyl iodide.*			
0·00000	2·2351	1·5943	28·14	117	28·1	0·00000	2·2377	1·5937	28·19	120	28·2
0·00643	2·2639	1·5929	28·70	116	28·2	0·00845	2·2739	1·5909	28·94	119	28·2
0·00807	2·2720	1·5921	28·86	116	28·2	0·01618	2·3111	1·5880	29·68	118	28·2
0·01724	2·3140	1·5899	29·66	115	28·2	0·02963	2·3661	1·5834	30·82	117	28·3
0·03278	2·3876	1·5863	31·05	113	28·2	0·06890	2·5313	1·5700	34·18	113	28·4
0·08108	2·6095	1·5755	35·14	108	28·5	0·17458	2·9512	1·5376	42·66	105	29
0·12688	2·8062	1·5653	38·71	104	29	0·44749	3·834	1 4704	61·50	97	33
0·49194	4·227	1·4949	63·26	91	35	0·81408	4·659	1·4050	83·17	94	37
0·58308	4·509	1·4854	68·15	90	36	1·00000	4·969	1·3792	93·36	93·4	38
0·00000	5·366	1·4329	87·73	87·7	40						

TABLE V.—(*continued*).

c_2.	ϵ.	$d_4^{20°}$.	P_{12}.	P_{E_2}.	P_{E_1}.	c_2.	ϵ.	$d_4^{20°}$.	P_{12}.	P_{E_2}.	P_{E_1}.
		n-Octyl iodide.						*β-Iodo-octane.*			
0·00000	2·2384	1·5942	28·19	125	28·2	0·00000	2·2350	1·5940	28·14	144	28·1
0·00548	2·2631	1·5914	28·73	124	28·2	0·00488	2·2621	1·5916	28·70	143	28·2
0·00919	2·2784	1·5896	29·07	124	28·2	0·00888	2·2865	1·5896	29·19	142	28·2
0·01333	2·2964	1·5876	29·45	123	28·2	0·01775	2·3327	1·5853	30·14	140	28·2
0·01555	2·3056	1·5866	29·66	123	28·2	0·03742	2·4405	1·5759	32·33	137	28·3
0·02853	2·3614	1·5804	30·87	122	28·2	0·07249	2·6277	1·5599	36·10	132	28·5
0·03018	2·3697	1·5795	31·04	122	28·2	0·16219	3·080	1·5227	45·13	126	30
0·04645	2·4395	1·5720	32·56	120	28·3	0·34834	3·915	1·4601	62·07	118	32
0·10709	2·6712	1·5458	37·74	114	28·6	0·67275	5·009	1·3811	87·75	112	37
0·11499	2·7123	1·5425	38·57	114	28·8	1·00000	5·770	1·3251	111·24	111·2	41
0·26620	3·218	1·4875	50·53	107	30						
0·47828	3·782	1·4276	65·75	102	33						
1·00000	4·670	1·3295	99·37	99·4	37						
		Lauryl iodide.						*Cetyl iodide.*			
0·00000	2·2367	1·5941	28·17	142	28·2	0·00000	2·2377	1·5938	28·19	159	28·2
0·00608	2·2621	1·5879	28·85	141	28·2	0·00515	2·2574	1·5860	28·84	158	28·2
0·01158	2·2859	1·5825	29·48	140	28·2	0·01051	2·2803	1·5778	29·56	157	28·2
0·02242	2·3310	1·5721	30·70	140	28·2	0·02122	2·3215	1·5621	30·94	156	28·2
0·04340	2·4149	1·5529	33·02	138	28·3	0·05181	2·4344	1·5214	34·89	154	28·3
0·08968	2·5825	1·5145	37·99	135	28·5	0·10118	2·5813	1·4653	40·97	152	28·6
0·17195	2·8368	1·4572	46·47	130	29	0·24559	2·8988	1·3484	58·23	147	29
0·40020	3·311	1·3459	68·15	124	31	0·55900	3·284	1·2139	94·29	144	31
0·75756	3·743	1·2448	100·42	122	32	1·00000	3·504	1·1207	143·01	143·0	32
1·00000	3·930	1·2015	121·81	121·8	33						

FIG. 4.

Partial molar polarisations at 20°. ($P_E = P_{E+A} + Z(\epsilon-1)^4/(\epsilon+2)^4 + Y/\epsilon$ *extrapolated to* $\epsilon = 1$ *and to* $\epsilon = \infty$.)



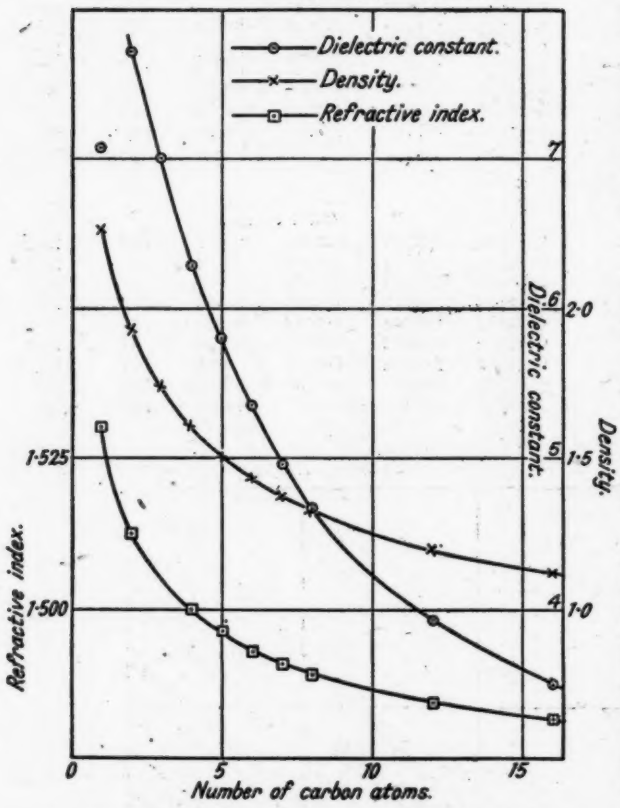
Experimental curve ——. Extrapolated curve – – – –.

from samples of the appropriate pure alcohols, and prepared by the method of Rieth and Beilstein (*Annalen*, 1863, **126**, 250). Purification was carried out as in section (A).

(D) sec.-*Butyl iodide, γ-iodopentane, and* β-*iodo-octane.* The procedure was similar to that described in section (C) except that, in the purification of the iodides, sodium carbonate was replaced by bicarbonate and the samples were dried with sodium sulphate.

FIG. 5.

Physical constants of primary alkyl iodides.



(E) tert.-*Butyl and -amyl iodides.* These were prepared as in section (D), except that they were washed only with ice-cold 1% sodium bicarbonate solution. Any residual iodine was removed by distillation at 100—150 mm. The purified tertiary iodides can be kept for a week without appreciable decomposition if stored in Pyrex flasks in the dark.

(F) n-*Hexyl and -heptyl iodides.* The appropriate alcohols, prepared from *n*-butyl alcohol and heptaldehyde respectively, were converted into the iodides and these were purified as in section (C).

(G) β-*Iodopentane.* This was prepared from a Kahlbaum sample of the alcohol. As only a small amount of the latter was available, Norris's method (*Amer. Chem. J.*, 1907, **38**, 639) was modified, the product being distilled with successive amounts of hydriodic acid (*d* 1·7) until the iodide had constant density. It was purified as in section (D).

The criteria of purity of these iodides are listed in Table IV, and compared with values recorded in the available literature. The only compound for which we find a significant difference from the published data is cetyl iodide. In Fig. 5 we have plotted our values for the physical constants of the primary iodides against the number of carbon atoms; from C_2 to C_{16} smooth curves are obtained. Delcourt's values for cetyl iodide, particularly for its refractive index, lie off the curves, and we conclude that our constants are more correct and our standard of purity correspondingly higher.

Results.—The experimental data, the polarisations of the mixtures (P_{12}), and the partial polarisations (P_{s2} for the iodides, P_{s1} for the carbon tetrachloride), obtained as intercepts of the tangents to the P_{12}-c_2 curves at the axes where c_2 is zero and unity, are recorded in Table V.

The authors' thanks are due to the Chemical Society for a grant.

THE UNIVERSITY, LEEDS, 2. [*Received, February 26th*, 1942.]

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60. *The Standardisation of Sodium Thiosulphate with Potassium Dichromate.*

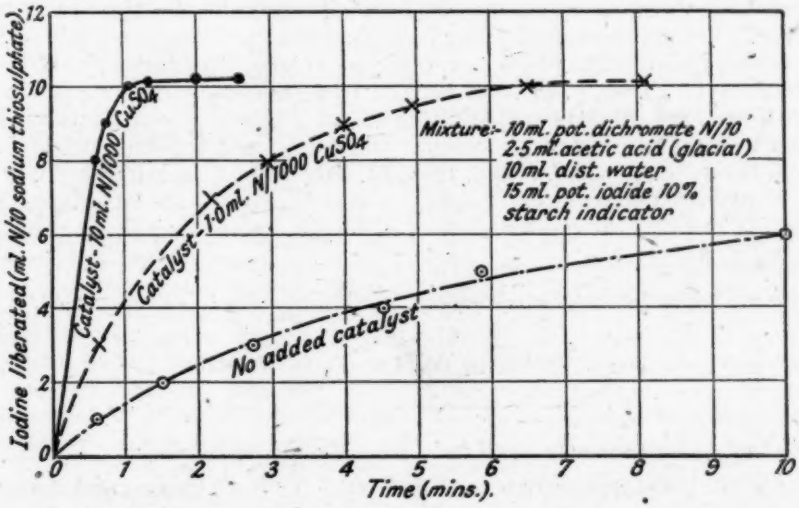
By B. DUDLEY SULLY.

Copper is shown to be a powerful catalyst for the reaction between potassium dichromate and potassium iodide. A new method of standardising sodium thiosulphate based on this fact avoids the use of a mineral acid with potassium iodide and is both more rapid and more accurate than the customary procedure.

POTASSIUM dichromate is readily obtainable in a high state of purity and is very stable in solution. It is therefore a desirable reference substance for the standardisation of thiosulphate solution. The reaction between potassium dichromate and potassium iodide liberates iodine very slowly unless the p_H of the solution is low: in the usual method 25 ml. of N/10-potassium dichromate, 30 ml. of 10% potassium iodide, and 6 ml. of concentrated hydrochloric acid are allowed to react in the dark for about 15 mins., during which the reaction is supposed to run to completion, and the iodine liberated is titrated with sodium thiosulphate with starch as indicator. The final solution is green owing to chromium salts, and in order to make the end-point more distinct it is customary to dilute the solution before titration.

The end-point is always quite sharp, but the reaction is not always quantitative, and variations of ½% are easily obtained. Snethlage (*Rec. Trav. chim.*, **1934**, **53**, 567) showed that the amount of iodine liberated is influenced by the rate of addition of potassium iodide, the concentration of acid, and even by the degree of illumination. It was further found that reproducible results are not obtainable except in dilute solution, and that sulphuric gives better results than hydrochloric acid.

It is well known that atmospheric oxygen liberates iodine from potassium iodide in the presence of a strong mineral acid, and hence it is preferable to work with a weaker acid, so the effect of acetic acid was investigated. 10·00 Ml. of N/10-potassium dichromate were acidified with 2·5 ml. of glacial acetic acid and diluted with 10 ml. of water. At zero time 15 ml. of a 10% solution of potassium iodide were added, and the liberated iodine was titrated immediately, the thiosulphate being added in quantities of 1.ml., and the time taken for the reappearance of the blue colour was noted with a stop-watch. The results obtained are shown in the Figure.


Iodine liberated (ml. N/10 sodium thiosulphate).
Time (mins.).
Catalyst - 10 ml. N/1000 CuSO4
Catalyst - 1·0 ml. N/1000 CuSO4
No added catalyst
Mixture:- 10 ml. pot. dichromate N/10
2·5 ml. acetic acid (glacial)
10 ml. dist. water
15 ml. pot. iodide 10%
starch indicator

The reaction was still not quite complete after one hour, so an attempt was made to catalyse it by addition of various salts. Iron and manganese had no appreciable action, but the effect of copper in very small amounts was remarkable: addition of 1 ml. of M/1000-copper sulphate solution liberated 90% of the iodine in 4 mins., and 10 ml. of the same solution afforded 90% of the iodine in 45 secs. Without a catalyst this degree of reaction requires 30 mins.

The reaction rate varies with the concentration, and to obtain the best results it is essential to avoid excessive dilution; for instance, 10·00 ml. of N/10-potassium dichromate, 2·5 ml. of glacial acetic acid, 10 ml. of M/1000-copper sulphate, and 15 ml. of 10% potassium iodide in 400 ml. of water liberated less than the equivalent of 0·1 ml. of N/10-sodium thiosulphate in 5 mins.; there was little increase in rate on adding 10·0 ml. of glacial acetic acid, and even on adding 1·0 ml. of concentrated hydrochloric acid the reaction was only 50% complete in 7½ mins. It is clearly inadvisable to dilute the solution until all the iodine has been liberated. Boiled-out water is necessary if mineral acids are used in the presence of potassium iodide.

From the foregoing considerations the following procedure is recommended. To 20·00 ml. of N/10-potassium dichromate in a 250-ml. conical flask add 5·0 ml. each of glacial acetic acid and N/1000-copper sulphate solution, the sides of the flask being washed down with 20·0 ml. of distilled water. Add 20·0 ml. of 15% potassium iodide and titrate the iodine as it is liberated with N/10-sodium thiosulphate solution, a little freshly made starch solution being added towards the end. The temperature should be about 20° and should not exceed about 25° in order to minimise the liberation of iodine by the action of atmospheric oxygen. The titration is complete in 3—4 mins. after addition of the iodide. The end-point when once reached is stable for a long time, the colour being that of a complex chromium acetate, and no difficulty is experienced in working to a fraction of a drop if a second flask containing the previous titration with an excess of sodium thiosulphate is used for comparison. 0·05 Ml. must be subtracted from the titration reading to allow for the iodine liberated by the copper sulphate catalyst. Individual titrations by different observers did not vary by more than 0·1%, and the mean value so obtained was 0·1% lower than that obtained by standardisation against copper wire.

For this standardisation the following method was used: it differs slightly from published methods in so far as it avoids formation of an excess of sodium acetate, the buffering effect of which results in a sluggish end-point. Polish a length of copper wire weighing approx. 1·4 g. with a little kieselguhr and water, dry it, wind it into a flat spiral, and weigh it. Transfer the spiral to a beaker, cover it with distilled water, add concentrated nitric acid very slowly until the copper just starts to dissolve, then allow it to stand without warming until dissolution is complete. Heat it slowly and remove nitrous fumes by short boiling. After cooling, neutralise

the excess of nitric acid with concentrated sodium or potassium carbonate solution until a slight precipitate is formed. This is dissolved immediately with a slight excess of N-hydrochloric acid, and the solution diluted to 200 ml. at 20°. 20·00 Ml. of this solution are measured into a conical flask, 0·5 g. of urea is added, and the solution boiled gently for 5 mins., then cooled and neutralised to turbidity with N-sodium hydroxide, avoiding excess. Add immediately 5·0 ml. of glacial acetic acid, dilute to 100 ml., and add 20 ml. of 15% potassium iodide. Titrate the liberated iodine with the sodium thiosulphate to be standardised. When near the end-point add 4 ml. of a 50% w./w. ammonium thiocyanate solution (Foote, *J. Amer. Chem. Soc.*, 1938, **60**, 1349). Complete the titration, using starch as indicator. The end-point should be stable for 5—10 mins.

The remarkable influence of such minute traces of copper on the reaction between potassium dichromate and potassium iodide makes it possible that in the past some investigators have fortuitously achieved good results owing to the presence of copper as an impurity in their reagents: 1 p.p.m. of copper in the titration solution accelerates the reaction about six-fold.

Copper has previously been used as a catalyst for many oxidation reactions but usually no quantitative data are given. The present reaction may be compared with the copper-catalysed reaction between ferric salts and sodium thiosulphate which, according to Feigl ("Qualitative Analysis by Spot Tests," Nordemann Publishing Co., 1939, p. 37), can be used to detect one part of copper in 2,500,000 parts. Steigmann (*Phot. Korr.*, 1934, **70**, 54) has shown that copper acts as a powerful catalyst for the formation of molybdenum-blue in a solution of ammonium molybdate and sodium thiosulphate stabilised by formaldehyde, and Brode (*Z. physikal. Chem.*, 1901, **37**, 257) made a quantitative study of the oxidation of the iodide ion by hydrogen peroxide catalysed by iron and copper. The latter found that iron is more effective than copper, and that the combined effect of both is greater than that to be expected from the influence of each metal separately.

I wish to thank my colleagues in this laboratory, particularly Mr. L. J. Edwards, B.Sc., for assistance in checking this work.

RESEARCH LABORATORY, A. BOAKE, ROBERTS & CO., LTD., LONDON, E. 15. [*Received, September 18th*, 1941.]

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61. *Synthesis of Compounds related to Mould Metabolic Products. Part I. 3 : 5-Dihydroxy-2-formylbenzoic Acid and 3 : 5-Dihydroxyphthalic Acid.*

By JOHN HOWARD BIRKINSHAW and ARTHUR BRACKEN.

Methyl 3 : 5-dihydroxybenzoate was converted by the Gattermann synthesis into *methyl 3 : 5-dihydroxy-2-formylbenzoate*, which on hydrolysis gave the free *acid*, and on mild potash fusion 3 : 5-dihydroxyphthalic acid.

THE mould *Penicillium stipitatum* Thom, when grown on a Czapek–Dox–glucose medium, produces a new acid, stipitatic acid, $C_8H_6O_5$ (Birkinshaw, Chambers, and Raistrick, *Biochem. J.*, 1942, **36**, in the press). This acid has certain properties which suggested that it might be a dihydroxyformylbenzoic acid, although other properties, notably its failure to yield aldehydo- or ketonic reactions, were not in accordance with this hypothesis. From the colour reaction with hypochlorite it appeared that stipitatic acid, if benzenoid in nature, would be a resorcinol derivative. The masking of the formyl group could only be ascribed to its being situated between a carboxyl and a hydroxyl group. Although it seemed unlikely that such a compound would not react with the usual aldehyde reagents, the synthesis of 3 : 5-*dihydroxy-2-formylbenzoic acid* was undertaken in order to exclude this possibility for the constitution of stipitatic acid. The synthetic product differed in m. p. and other properties from stipitatic acid.

Benzoic acid was converted into the disulphonate substantially by Brunner's method (*Monatsh.*, 1928, **50**, 216). Potash fusion of the dipotassium disulphonate (Barth and Senhofer, *Annalen*, 1871, **159**, 222, give inadequate details) afforded 3 : 5-dihydroxybenzoic acid in much better yield than that claimed by Graves and Adams (*J. Amer. Chem. Soc.*, 1923, **45**, 2439), who fused the acid barium salt of the disulpho-acid with potassium hydroxide. Moreover Brunner's method of sulphonation avoids the use of an autoclave.

Methyl 3 : 5-dihydroxybenzoate was subjected to a Gattermann reaction, following the method of Shah and Laiwalla (J., 1938, 1828), and *methyl 3 : 5-dihydroxy-2-formylbenzoate* was thus obtained. On cold alkaline hydrolysis it afforded 3 : 5-dihydroxy-2-formylbenzoic acid, although the possibility is not excluded that it also exists in the tautomeric hydroxyphthalide form. Both the methyl ester and the acid gave immediate precipitates of the corresponding *hydrazones* with 2 : 4-dinitrophenylhydrazine hydrochloride in 2N-hydrochloric acid.

Although, in accordance with the usual course of the Gattermann reaction, the formyl group should

occupy a position *op* to the two hydroxyl groups, yet in view of the production of methyl 2 : 4-dihydroxy-3-formylbenzoate from the 2 : 4-dihydroxy-ester as shown by Shah and Laiwalla (*loc. cit.*) it was necessary to obtain definite evidence of the point of entry of the formyl group in the present case. This was done by conversion of the aldehydo- into a carboxyl group. Potash fusion of the synthetic ester under mild conditions (cf. Tiemann and Reimer, *Ber.*, 1877, **10**, 1570; Tiemann and Lewy, *ibid.*, p. 2210) gave a mixture of acids, from which 3 : 5-dihydroxyphthalic acid was readily separated as the lead salt. The acid after purification was identical with 3 : 5-dihydroxyphthalic acid obtained from *Penicillium brevi-compactum* Dierckx by Oxford and Raistrick (*Biochem. J.*, 1932, **26**, 1902). Further proof of its identity was obtained by conversion into 3 : 5-dimethoxyphthalic anhydride, which agreed in m. p. and mixed m. p. with the authentic product prepared by Fritsch's method (*Annalen*, 1897, **296**, 357) from 3 : 5-dimethoxybenzoic acid.

Although the synthesis of 3 : 5-dimethoxyphthalic acid and its anhydride were described by Fritsch, the present account appears to be the first recorded synthesis of 3 : 5-dihydroxyphthalic acid, which has hitherto been encountered only as a metabolic product of *P. brevi-compactum*.

Experimental.

Dipotassium Benzoic acid-3 : 5-disulphonate.—Benzoic acid (100 g.) was sulphonated with fuming sulphuric acid and chlorosulphonic acid at ordinary pressure according to the method of Brunner (*loc. cit.*). During the second and the third heating (in the presence of chlorosulphonic acid) the mixture was refluxed for 2 hours each time at a bath temperature of 245° (the highest temperature which could be obtained owing to the volatility of the chlorosulphonic acid); the head was then changed to downward air-condenser and chlorosulphonic acid was allowed to distil until the bath temperature reached 260°. As most of the excess of chlorosulphonic acid was thus removed, the amount of barium carbonate required for subsequent neutralisation was considerably reduced. The yield of air-dried crystalline dipotassium salt (of unknown water content) was 286 g.

3 : 5-Dihydroxybenzoic Acid.—The disulphonate (20 g.) was heated with 80 g. of potassium hydroxide and 15 ml. of water in a nickel crucible. The metal-bath temperature was raised as rapidly as frothing would permit to 360° with frequent stirring and maintained at that point for ¾ hour. The melt was pink in the early stages, later becoming colourless, then yellowish; it gradually acquired the colour and consistency of pea-soup. When the heating was finished, the melt was dissolved in water, and the solution acidified and extracted with ether. The crude extract was crystallised from water. The yield of anhydrous acid (dried at 105°) was 6·5 g., m. p. 234°. Thus the yield from 100 g. of benzoic acid is 93 g.

Methyl 3 : 5-Dihydroxybenzoate.—The dry acid (32·4 g.) was refluxed with methyl alcohol (200 ml.) containing concentrated sulphuric acid (5 ml.) for 16 hours. Then 150 ml. of the alcohol were distilled, and 100 ml. of water added to the residue. The solution became cloudy and after 16 hours at 0° had deposited a mass of crystals. These were collected and washed with water; yield 26·3 g., m. p. 165°. The filtrate was extracted with ether; the extract, after being washed with aqueous sodium bicarbonate, gave further crystals, which were recrystallised from aqueous methyl alcohol, giving a total yield of 32·7 g.

Methyl 3 : 5-Dihydroxy-2-formylbenzoate.—To methyl 3 : 5-dihydroxybenzoate (32·7 g.) and dry ether (300 ml.), cooled in a freezing mixture, anhydrous zinc cyanide (46 g.) was added; the mixture was stirred while a chilled solution of anhydrous aluminium chloride (52 g.) in dry ether (200 ml.) was introduced. Dry hydrogen chloride was passed in until the mixture was saturated (about 4 hrs.). After standing overnight, the ether was decanted, and the semi-solid washed with dry ether. A solution of the residue in 100 ml. of cold water, after being heated on the water-bath for 20 minutes and cooled, deposited colourless crystals (10 g.) and on recrystallisation from water *methyl 3 : 5-dihydroxy-2-formylbenzoate* separated in needles, m. p. 163·5°, not raised by sublimation. It gave a deep port-wine colour with ferric chloride in water or alcohol (Found: C, 54·9; H, 4·3; OMe, 14·8. $C_9H_8O_5$ requires C, 55·1; H, 4·1; OMe, 15·8%).

The *2 : 4-dinitrophenylhydrazine* (0·2 g.), prepared from the ester (0·1 g.) in 3 ml. of alcohol and an excess of 2 : 4-dinitrophenylhydrazine hydrochloride in hydrochloric acid, crystallised from alcohol, in which it was only slightly soluble, in scarlet needles, m. p. 293° (decomp.) when heated from room temperature, 297° (decomp.) when introduced into the bath at 288° (Found: C, 47·7, 47·8; H, 3·0, 2·9; N, 14·7; OMe, 8·8. $C_{15}H_{12}O_8N_4$ requires C, 47·9; H, 3·2; N, 14·9; OMe, 8·3%).

3 : 5-Dihydroxy-2-formylbenzoic Acid.—A solution of the methyl ester (1 g.) in 15% aqueous sodium hydroxide (16 ml.) was acidified with 5N-hydrochloric acid after 3 days. The cream-coloured precipitate was washed and dissolved in saturated sodium hydrogen carbonate solution (10 ml.). Addition of an excess of 5N-hydrochloric acid precipitated *3 : 5-dihydroxy-2-formylbenzoic acid* in needles (0·70 g.). Recrystallised twice from a little water (norit), in which it was very soluble at the b. p., it formed irregular colourless prisms, m. p. 233° to a black fluid. The acid gave a pale yellow colour in alkaline solution and, like the ester, a deep port-wine colour with aqueous ferric chloride [Found: C, 52·4, 52·3; H, 3·5, 3·6; equiv. by titration, 91·6. $C_8H_6O_5$ requires C, 52·8; H, 3·3%; equiv. (dibasic), 91·1].

The *2 : 4-dinitrophenylhydrazone*, obtained from an aqueous solution of the acid and an excess of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid, crystallised from alcohol in microscopic, elongated, hexagonal, crimson tablets, m. p. 301° (decomp.). It retained rather more than 1 mol. of water when dried in a vacuum at room temperature, but this was lost at 150° in a high vacuum (Found: loss at 150° in a high vacuum,

5·8. $C_{14}H_{10}O_8N_4.H_2O$ requires H_2O, 4·7%. Found for anhydrous material: C, 46·3; H, 2·9; N, 15·2. $C_{14}H_{10}O_8N_4$ requires C 46·4; H, 2·8; N, 15·5%).

3 : 5-*Dihydroxyphthalic Acid.*—A mixture of methyl 3 : 5-dihydroxy-2-formylbenzoate (1 g.), potassium hydroxide (10 g.), and water (2 ml.) in a bath at 170° was heated with constant stirring at 180° for 10 minutes and at 190° for 15 minutes; the test for aldehyde was then almost negative. The product was dissolved in water, acidified, and extracted with ether. The syrupy extract was dissolved in water (50 ml.), neutralised with sodium hydroxide (external indicator), and treated with excess of normal lead acetate solution. The precipitate was washed and treated with sulphuric acid. The filtrate from the lead sulphate was extracted with ether, which afforded a crystalline solid (0·46 g.). Recrystallisation from ethyl acetate–light petroleum gave elongated prisms (0·14 g.), m. p. 184—185°, remelting at 206—208°, not depressed by 3 : 5-dihydroxyphthalic acid, m. p. 188°, remelting at 208—210°, obtained by Oxford and Raistrick (*loc. cit.*) from *Penicillium brevi-compactum*; further, the red colours given by the two products with aqueous ferric chloride were identical. Further confirmation of identity was obtained by conversion of the synthetic acid into the dimethyl ether of the anhydride. The synthetic acid (0·1 g.) was methylated with an excess of diazomethane in ether (left overnight) and the ester groups were hydrolysed by boiling with 2N-sodium hydroxide for 2 hours. The extracted acid was heated with boiling acetic anhydride for 30 minutes. The acetic anhydride was then removed in a vacuum, and the product sublimed. It had m. p. 146—148°, not depressed by sublimed 3 : 5-dimethoxyphthalic anhydride prepared by Fritsch's method (*loc. cit.*).

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE. [*Received, January 15th*, 1942.]

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62. *Molecular Dissymmetry due to Symmetrically Placed Hydrogen and Deuterium. Part III. The Attempted Resolution of 4 : 4′-Dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine. A Method for the Determination of Deuterium in Organic Compounds.*

By G. R. CLEMO and G. A. SWAN.

Attempts to resolve 4 : 4′-dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine have been unsuccessful. The Harteck method for the determination of deuterium has been developed for the estimation of the relative proportions of hydrogen and deuterium in organic compounds.

PREVIOUS work (Clemo, Gardner, and Raper, J., 1939, 1958) resulted in resolution of 4-chloro-, 4-bromo-, and 4-iodo-benzhydrylamines, but was unsuccessful in that of the 4-methyl compound. Failure to resolve α-pentadeuterophenylbenzylamine has been recorded by Adams and Tarbell (*J. Amer. Chem. Soc.*, 1938, **60**, 1260) and by Clemo and Swan (J., 1939, 1960). Nevertheless, we decided to prepare 4 : 4′-*dibromo*-2 : 3 : 5 : 6-*tetradeuterobenzhydrylamine*, and to attempt to resolve it, hoping that the presence of the symmetrically placed bromine atoms in the molecule, together with the dissymmetry due to the difference between hydrogen and deuterium, would render resolution practicable.

As a preliminary, the preparation of 4 : 4′-*dibromobenzhydrylamine* was investigated by the method used by Clemo, Gardner, and Raper for preparing 4-bromobenzhydrylamine, but the experimental conditions were modified so as to minimise the risk of exchange, when applied to the preparation of the "heavy" base: the time of heating with formamide was reduced, and the hydrolysis carried out by means of alkali instead of acid.

Resolution of the 4 : 4′-dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine was attempted by crystallisation of the *d*-hydrogen tartrate and of the *d*-bromocamphorsulphonate from alcohol. No change in the specific rotation of the salt was observed, and the recovered base was optically inactive. This work was completed some time ago. We hope to attack the problem along a new line when opportunity occurs.

The relative proportions of hydrogen and deuterium in water can be conveniently estimated by a method making use of the considerable difference in thermal conductivity between the vapours of protium oxide and deuterium oxide, in equilibrium with the corresponding ice at a constant temperature. This method has several advantages over other methods: the effect on which it depends is very favourable because it is really the resultant of two effects which reinforce one another; deuterium oxide has a lower vapour pressure than protium oxide, so the amount of the former in the vapour phase is less than that of the latter, and, moreover, the thermal conductivity of duterium oxide vapour is lower than that of protium oxide vapour. Also the method requires only a very small quantity of water and it has a number of advantages over that of Farkas (*Proc. Roy. Soc.*, 1934, *A*, **144**, 467) which depends on thermal conductivity measurements on the purified hydrogen gas formed by decomposition of the water by passage over a hot tungsten wire. In the method we use, the latter processes and the pressure measurement are eliminated. It was suggested by Harteck (*Z. Elektrochem.*, 1938, **44**, 4), but a detailed description of the apparatus

has not been published. We have employed this method for estimating the proportion of deuterium in the water formed by combusting " heavy " compounds in a current of oxygen, with platinum contacts. Although only 0·5 mg. of water was used in each determination, sufficient of the compound was usually combusted to give at least 4 mg. of water, so that several successive values could be obtained. When relatively large amounts of water were used, consistent results were readily obtained; but when only a very small amount (*e.g.*, 2 or 3 mg.) was available, each successive determination was slightly higher than the previous one, doubtless because protium oxide, being slightly more volatile than deuterium oxide, is enriched in the vapour, so that the residual liquid has a slightly higher deuterium content than the original water. Although this effect had been observed by Harteck and by Geib (*ibid.*, p. 7), they do not appear to have applied a correction for it; the following method was therefore adopted.

If C represents the ratio of protium atoms to deuterium atoms in the gas divided by this ratio in the liquid, it is given (Urey and Teal, *Rev. Mod. Physics*, 1935, **7**, 48) by

$$C = \frac{2AB + (ABkK)^{\frac{1}{2}}}{2 + (ABkK)^{\frac{1}{2}}} \cdot \frac{2 + (BK)^{\frac{1}{2}}}{2B + (BK)^{\frac{1}{2}}}$$

where A is the ratio of the vapour pressures of pure H_2O and D_2O and B is the ratio of their mole-fractions in the liquid; $k = p_{12}^2/p_{11}p_{22}$, where p_{12}, p_{11}, and p_{22} are the vapour pressures of the pure liquids HDO, H_2O, and D_2O respectively; and K is the equilibrium constant of the reaction $H_2O + D_2O \rightleftharpoons 2HDO$. For the gaseous reaction at 25°, Topley and Eyring (*J. Chem. Physics*, 1934, **2**, 217) have calculated K to be 3·26; this will also be the value for liquid water if $k = 1$, which is approximately the case. The value of A was taken as 1·149 (Lewis and Macdonald, *J. Amer. Chem. Soc.*, 1933, **55**, 3058). Then the value of C is approximately 1·075.

The volume of the " pipette " (the space bounded by taps 10, 11, 12, 13, and 17; see Fig. 1), by means of which an approximately equal amount of water vapour was measured for each determination, was about 35 c.c., so that approximately 0·5 mg. of water was used. The volume of the tube (14, 15, or 16) in which the liquid water was contained was about half this amount. Consider a sample of water containing a g.-atoms of protium and b g.-atoms of deuterium. Suppose that the vapour produced (in the tube itself and in the " pipette ") contains $3x$ g.-atoms of protium and $3y$ g.-atoms of deuterium. Of this, $\frac{2}{3}$ will be used in the determination (and pumped out afterwards) and the remaining $\frac{1}{3}$ will be left in the tube. Thus $(x/y)/[(a - 3x)/(b - 3y)] = 1·075$ and the ratio of protium to deuterium in the residual liquid water will be $(a - 3x)/(b - 3y)$, whereas that in the original water was a/b; $2(x + y)$ represents the amount of water used in each determination (*i.e.*, 0·5 mg.) and $(a + b)$ represents the total amount of water available. Then

$$1/\left(1 + \frac{a - 3x}{b - 3y}\right) - 1/\left(1 + \frac{a}{b}\right) = \frac{\Delta}{100}$$

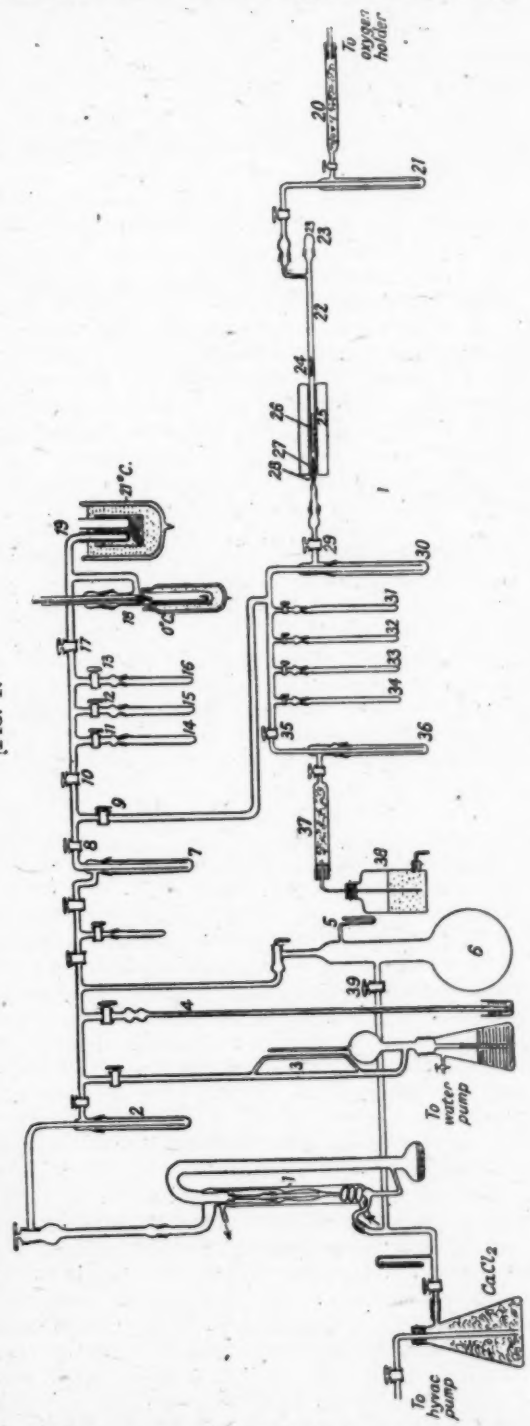


FIG. 1.

where Δ is the excess of the observed over the true percentage of deuterium. The value of Δ is a maximum when the proportion of deuterium is in the region of 50 atoms %; in the region of 0% or 100%, the value is very small. The value of Δ also increases as the weight of water available decreases; *e.g.*, for a 1 : 1 mixture, the value is 0·6 when only 2 mg. water are available, and about 0·35 for 4·5 mg. water. When several successive measurements are made from the same sample of water, the correction for the final measurement is obtained by summation of the separate Δ values (gradually increasing, on account of the amount of water diminishing); *e.g.*, if 4 mg. of water of deuterium content 50 atoms % are used, then the correction for the fourth measurement would be approximately (0·4 + 0·45 + 0·5 + 0·55), *i.e.*, 1·9%. In the calibration, a relatively enormous amount of water is used, so no appreciable error arises on account of fractionation.

Experimental.

Formo-4 : 4′-dibromobenzhydrylamide.—4 : 4′-Dibromobenzophenone (Hoffmann, *Annalen*, 1891, **264**, 163) (2 g.) was heated with formamide (6 c.c.) for 6 hours at 175°, and the mixture poured into water; the product was filtered off, washed with water, dried, and recrystallised from methanol, forming colourless prisms (1·8 g.), m. p. 159° (Found: C, 45·3; H, 3·3; N, 4·0. $C_{14}H_{11}ONBr_2$ requires C, 45·5; H, 3·0; N, 3·8%).

4 : 4′-Dibromobenzhydrylamine.—The above formyl derivative (1 g.) was heated with potassium hydroxide (1·5 g.) in methanol (8 c.c.) for 6 hours on the water-bath. After distillation of most of the methanol and pouring the residue into water, the base was taken up in ether, the extract dried with potassium carbonate, the ether removed, and the product recrystallised from light petroleum (b. p. 60—80°), forming colourless prisms, m. p. 76° (Found: C, 45·9; H, 2·8; N, 4·4. $C_{13}H_{11}NBr_2$ requires C, 45·7; H, 3·2; N, 4·1%). The *hydrochloride* formed colourless needles (Found: C, 41·7; H, 3·7. $C_{13}H_{12}NClBr_2$ requires C, 41·4; H, 3·2%). The *d*-hydrogen tartrate has m. p. 210—211°, $[\alpha]_D^{18°}$ +9·5° (*l* = 2, *c* = 2, in methanol); the *d*-bromocamphorsulphonate has m. p. 260—262°, $[\alpha]_D^{18°}$ +46·4° (*l* = 2, *c* = 2, in methanol).

4 : 4′-Dibromo-2 : 3 : 5 : 6-tetradeuterobenzophenone.—Bromopentadeuterobenzene (0·40 g.), *p*-bromobenzoyl chloride (0·55 g.), freshly sublimed aluminium chloride (0·38 g.), and dry carbon disulphide (0·3 c.c.) were mixed in a small flask fitted with a ground-in condenser, leading to a trap containing potassium hydroxide (to remove the evolved deuterium chloride from the sphere of chemical reaction and hence minimise the chance of exchange occurring). After being heated for 22 hours on the water-bath, the mixture was cooled, decomposed by addition of ice and dilute hydrochloric acid, and warmed on the water-bath for 10 minutes to hydrolyse excess of *p*-bromobenzoyl chloride. The ketone was taken up in chloroform, the extract washed with water and with sodium hydroxide solution, dried with sodium sulphate, the chloroform removed, and the product recrystallised from ethanol, forming colourless leaflets (0·55 g.), m. p. 172—173° (Found: C, 45·2; water, 22·1. $C_{13}H_4D_4OBr_2$ requires C, 45·3; water, 22·1%. Isotopic analysis. Found: 47 atoms % D. $C_{13}H_4D_4OBr_2$ requires 50 atoms % D).

Formo-4 : 4′-dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamide.—The above ketone (0·55 g.) was heated with formamide (1·7 c.c.) for 6 hours at 175°. After being poured into water, the product was filtered off, washed with water, dried, and recrystallised from methanol, affording colourless prisms (0·50 g.), m. p. 158—159° (Found: C, 44·7; water, 29·5. $C_{14}H_7D_4ONBr_2$ requires C, 45·0; water, 27·6%. Isotopic analysis. Found: 36·8 atoms % D. $C_{14}H_7D_4ONBr_2$ requires 36·4 atoms % D).

4 : 4′-Dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine.—The above formyl derivative (0·50 g.) was heated with potassium hydroxide (0·7 g.) in methanol (4 c.c.) for 3½ hours on the water-bath. After isolation as for the undeuterated compound (see above), the *base* crystallised from light petroleum (b. p. 60—80°) as colourless prisms (0·37 g.), m. p. 75—76° (Found: C, 45·5; water, 30·0. $C_{13}H_7D_4NBr_2$ requires C, 45·2; water, 29·9%. Isotopic analysis. Found: 36 atoms % D. $C_{13}H_7D_4NBr_2$ requires 36·4 atoms % D). The *d*-hydrogen tartrate has m. p. 210—212°, $[\alpha]_D^{18°}$ +9·3° (*l* = 2, *c* = 2·5, in methanol), $[\alpha]_{5461}^{18°}$ +10·5°, $[\alpha]_{4358}^{18°}$ +15·3° (*l* = 2, *c* = 2, in methanol). The *d*-bromocamphorsulphonate has m. p. 260—262°, $[\alpha]_D^{18°}$ +45·9° (*l* = 2, *c* = 2, in methanol).

Attempted resolution. 0·57 G. of the *d*-hydrogen tartrate was recrystallised 4 times from 95% ethanol, 0·10 g. remaining. The specific rotation $[\alpha]_{4358}^{18°}$ remained constant within the limits of experimental error at +15·3° (*e.g.*, successive values, 15·1°, 15·0°, 15·7°), as did the m. p. The recrystallised tartrate (0·10 g.) was shaken with dilute sodium hydroxide solution, the base extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue recrystallised from light petroleum (b. p. 60—80°), giving 60 mg. of base, m. p. 75—76°. When examined in the micropolarimeter tube, this gave $\alpha_D^{18°}$ 0·00° ± 0·01° (*l* = 0·5, *c* = 8·6, in ethanol). The tartrate recovered after many recrystallisations was analysed isotopically (Found: 23·3 atoms % D, $C_{17}H_{13}D_4O_6NBr_2$ requires 23·5 atoms % D).

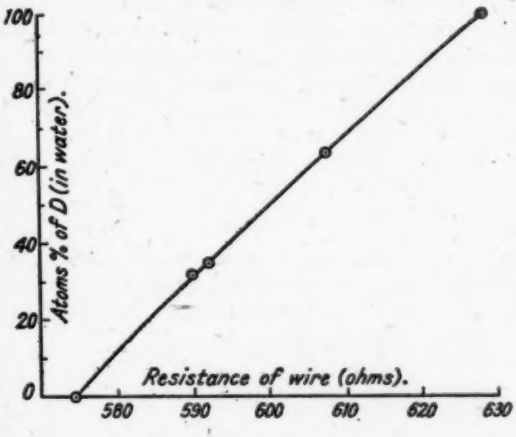
0·67 G. of the *d*-bromocamphorsulphonate was recrystallised 8 times from 90% ethanol, after which 0·10 g. remained. The base (recovered as described above) had m. p. 76°, and gave $\alpha_D^{18°}$ 0·00° ± 0·02° (*l* = 0·5; *c* = 9·8, in ethanol). This salt was also recrystallised 4 times from 10% ethanol, the specific rotation $[\alpha]_D^{18°}$ remaining vitually constant (*e.g.*, successive values, 45·9°, 45·8°, 45·9°). The recovered base had m. p. 75—76°, $\alpha_D^{18°}$ 0·00° ± 0·01° (*l* = 0·5, *c* = 6·8, in ethanol). The lower limit of any specific rotation which could have been detected with certainty on the recovered base is estimated at about 0·5°.

Isotopic Analysis.—The apparatus used is shown diagramatically in Fig. 1. The " heavy " compounds were combusted, by a micro-method, in a stream of pure oxygen (rate of flow 3·5 c.c./min.) from which the last

traces of moisture had been removed by passage through a trap (21) cooled in liquid air. The combustion tube (22) was of Jena glass, 60 cm. long and 10 mm. in diameter; it contained two platinum contacts, each made from a piece of foil 5 × 5 cm., which were heated to 600° by an electric furnace, followed by a roll of silver wool, 6 cm. long, to remove halogens. The water formed was collected in a trap (30) cooled in solid carbon dioxide–alcohol; entry of moisture from the end of the train through which the oxygen escaped was prevented by drying-tubes and a second liquid-air trap (36). This water was purified by repeated pumping-out, while cooled with solid carbon dioxide, and redistillation until free from dissolved gases (about four distillations). A three-stage mercury diffusion pump was used, and all taps and ground joints lubricated with apiezon L grease. Whenever possible, sufficient of the compound was used to give 4 mg. of water on combustion; but measurements could be carried out with smaller quantities, although the results so obtained were not quite so accurate.

In the measuring section of the apparatus, a constant temperature of about −21° was obtained by using an aluminium block in which was drilled a cylindrical cavity, into which the condensation-tube (19) just fitted; the block was dipped into liquid air and then immersed in a saturated sodium chloride solution at −20°, contained in a large Dewar vessel. A layer of cryohydrate thus formed around the block, which then acted as a thermostat. We, however, found this arrangement (originally suggested by Harteck) inconvenient, so we subsequently employed a block in which two cylindrical cavities were drilled, one to fit the condensation-tube, and the other considerably wider. This block was not dipped into liquid air, but was simply immersed in a previously cooled saturated solution of " AnalaR " sodium chloride in distilled water, contained in a well-lagged, silvered Dewar vessel 22 cm. deep and 11 cm. in diameter, and then liquid air was poured into the wider cavity until a sufficiently thick layer of cryohydrate had been formed. When so much of the cryohydrate had melted that the temperature was no longer constant, it was only necessary to pour in some more liquid air to restore the cryohydrate. After liquid air had been poured in, the block was allowed to stand for ½—1 hour to regain temperature equilibrium, before any measurements were carried out.

FIG. 2.



The measuring wire was of platinum, 5μ in diameter and 6 cm. long; it was kept taut by a spiral about 15 mm. long, made of platinum wire 0·05 mm. in diameter. A Sullivan rotary-switch Wheatstone Bridge was used; the rheostat arm consisted of four dials (having a range of 1—11,110 ohms), and the four pairs of ratio arm coils had resistances of 10, 100, 1,000, and 10,000 ohms respectively. A Sullivan Universal Galvanometer of resistance 132·2 ohms (20°) was employed in conjunction with a shunt of 10,000 ohms. The battery, of 4 volts, consisted of Fuller " block " type accumulators insulated so as to keep their temperature (and hence their E.M.F.) constant. Immediately after the water had been admitted to the condensation-tube, the accumulator switch was closed; 2 mins. later the bridge reading was taken, and measurements were repeated at intervals of 1 min. until the reading had reached a constant value (this usually occurred after the second reading). The ice was then pumped out from the condensation-tube, at least 5 mins. being allowed. Another sample of the same specimen of water was then introduced, and the measurements repeated; three or four sets of measurements were usually carried out on each specimen of water, the last one (with correction for fractionation) being taken for the final result. Before a new sample of water was introduced at least 15 mins. were allowed for pumping out. A current must never be passed through the measuring wire when the space surrounding it is completely evacuated, otherwise the wire becomes overheated, the nature of its surface changes, and hence the calibration is vitiated. The calibration was carried out by using mixtures of deuterium oxide and protium oxide of known composition. The graph of deuterium concentration (0—100%) plotted against resistance was almost linear (Fig. 2).

Before carrying out an isotopic analysis on a " heavy " compound (some of which contained halogen and nitrogen), the corresponding " light " compound was combusted, and measurements were carried out on the resulting " light " water, to ensure that the result on the " heavy " compound would not be inaccurate on account of impurities in the water. The results obtained on the compounds investigated here, as well as those concerned in a following paper, agreed fairly well with those given by pure " light " water.

The accompanying table gives a typical series of results :

Substance.	Weight (mg.). Substance.	Water formed.	Resistance (ohms).	% of D.
H_2O	—	—	575·9	—
$C_{14}H_{11}ONBr_2$	15	4	575·4, 575·5	—
D_2O	—	—	—, 628·7, 629·2	—
$C_{14}H_7D_4ONBr_2$	15	4	595·2, 593·6, 593·7	38·0 − 1·2 = 36·8
H_2O	—	—	—, —, 575·9	—
$C_{13}H_9D_3N,C_4H_6O_6$	9	4	587·5, 588·1, 588·0	27·5 − 1·0 = 26·5
$C_{13}H_7D_4NBr_2,C_4H_6O_6$	15	4·5	586·0, 586·3, 586·3	23·9 − 0·65 = 23·25
H_2O	—	—	—, 575·8, 575·9	—

A full description of the apparatus and of its use is to be found in a Ph.D. Thesis by one of us (G. A. S.) in our Library.

Our thanks are due to Dr. J. Weiss for invaluable advice on the isotopic analyses; to Imperial Chemical Industries for a grant towards the purchase of deuterium oxide; and to the Department of Scientific and Industrial Research for a maintenance grant to one of us (G. A. S.).

UNIVERSITY OF DURHAM, KING'S COLLEGE, NEWCASTLE-UPON-TYNE. [*Received, February 21st*, 1942.]

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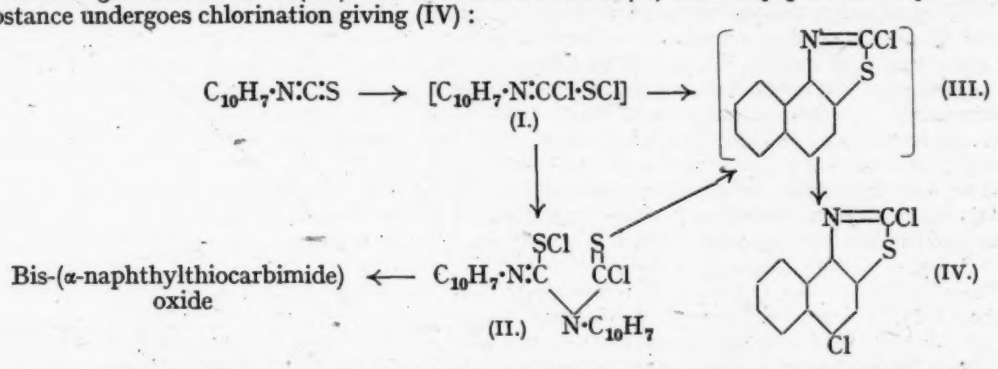
63. *The Action of Chlorine on Aryl Thiocarbimides and the Reactions of Aryl* iso*Cyanodichlorides. Part III. The Addition of Chlorine to α-Naphthylthiocarbimide and the Structure of the Compounds obtained.*

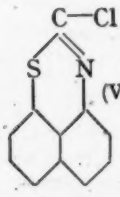
By G. MALCOLM DYSON and THOMAS HARRINGTON.

The action of chlorine upon α-naphthylthiocarbimide yields an unstable chloro-addition compound, which forms *bis-(α-naphthylthiocarbimide) oxide* when exposed to the air. Further addition of chlorine produces 2 : 4′-*dichloronaphtha*(1′ : 2′ ; 4 : 5)*thiazole* and prolonged chlorination yields a compound of empirical formula $C_{11}H_2NCl_5S$. α-Naphthyl *iso*cyanodichloride was not obtained.

WHEN chlorine is passed into a chloroform solution of α-naphthylthiocarbimide, the additive compound (I), which is presumably the first product formed, may either pass into (II) or undergo loss of hydrogen chloride to give the thiazole (III). It is considered that (II) also may pass directly into (III). This substance undergoes chlorination giving (IV) :



Compound (II) is rapidly converted by moisture into the corresponding *oxide* (cf. Dyson and Harrington, J., 1940, 191; this vol., p. 150). That the product of ring-closure of (I) is probably the thiazole (III) and not the *peri*naphthathiazine (V) is based on the observation that 2-phenyl*peri*naphthathiazine (V with Ph for Cl; Reissert, *Ber.*, 1922, **55**, 858) is not identical with the product of oxidation of thiobenz-α-naphthalide (cf. Jacobson, *Ber.*, 1887, **20**, 1898), which is therefore evidently 2-phenylnaphtha(1′ : 2′ : 4 : 5)thiazole (III with Ph for Cl).



(V.)

The position of the nuclear chlorine atom in (IV) is established by the preparation of this compound by the action of chlorine on 4-*chloro-α-naphthylthiocarbimide*.

Prolonged action of chlorine on α-naphthylthiocarbimide gives a substance of probable formula $C_{11}H_2NCl_5S$.

EXPERIMENTAL.

α-Naphthylthiocarbimide.—α-Naphthylamine (145 g.) in chloroform (500 ml.) was added during 2 hours to thiocarbonyl chloride (115 g.) suspended by vigorous stirring in water (800 ml.). Stirring was continued for a further ½ hour. The white solid formed was removed (a portion crystallised from alcohol had m. p. 215°, and was probably *s*-di-α-naphthylthiourea, recorded m. p. 212—214°), the chloroform solution separated and dried by calcium chloride, and the chloroform and the excess of thiocarbonyl chloride distilled off from a water-bath. An oil remained which set solid on cooling and crystallised from aqueous acetone in white needles (100 g.), m. p. 57°.

4-*Chloro-α-naphthylthiocarbimide.*—4-Chloro-α-naphthylamine (18 g.) (Reverdin and Crépieux, *Ber.*, 1900, **33**, 682) in chloroform (100 g.) was added slowly with shaking to thiocarbonyl chloride (12 g.) suspended in water (100 ml.). The mixture turned apple-green and a solid was deposited; this crystallised from alcohol (charcoal) in pale blue needles (5 g.), m. p. 230° (decomp.), and was probably *s*-di-(4-chloro-α-naphthyl)thiourea.

The chloroform layer was separated and dried over calcium chloride, and the chloroform and the excess of

thiocarbonyl chloride distilled off. The residual oil solidified on cooling and then formed colourless needles (14 g.), m. p. 87°, from acetone (Found: N, 6·3; S, 14·4; Cl, 16·3. $C_{11}H_6NClS$ requires N, 6·4; S, 14·6; Cl, 16·1%).

Bis-(α-naphthylthiocarbimide) Oxide.—α-Naphthylthiocarbimide (50 g.) in chloroform (100 g.) was slowly treated with chlorine for 3 hours; the increase in weight was 40 g. Yellow needles were deposited, which crumbled within 5 minutes after collection to a white powder, m. p. 79°, at the same time evolving hydrogen chloride. It was obtained from alcohol in white needles (30 g.), m. p. 80° (Found: N, 7·2. $C_{22}H_{14}ON_2S_2$ requires N, 7·3%).

2 : 4′-Dichloronaphtha(1′ : 2′ : 4 : 5)thiazole.—(1) α-Naphthylthiocarbimide (50 g.) in chloroform (100 g.) was treated with chlorine more rapidly than in the preparation of bis-(α-naphthylthiocarbimide) oxide; the increase in weight was 50 g. in 2 hours and hydrogen chloride was evolved. After 12 hours the pink solid was collected and crystallised from alcohol, forming blue needles (25 g.) which became colourless after prolonged boiling with alcohol and charcoal; m. p. 113°. The chloroform filtrate deposited a further 5 g. of *2 : 4′-dichloronaphtha(1′ : 2′ : 4 : 5)thiazole* (Found: C, 51·7; H, 2·3; N, 6·0; S, 12·8; Cl, 28·5. $C_{11}H_5NCl_2S$ requires C, 52·0; H, 2·0; N, 5·5; S, 12·6; Cl, 28·0%).

Prolonged addition of chlorine to α-naphthylthiocarbimide in chloroform produced a solution which deposited yellow crystals on standing. These were obtained from benzene in small white needles, m. p. 235° (decomp.) (Found: N, 3·9. $C_{11}H_3NCl_4S$ requires N, 3·9%).

(2) In order to confirm its structure 2 : 4′-dichloronaphtha(1′ : 2′ : 4 : 5)thiazole was prepared as follows: 4-Chloro-α-naphthylthiocarbimide (10 g.) in chloroform (50 g.) was treated with chlorine for 2 hours so that the increase in weight was 5 g. The needles deposited after 2 days had m. p. 110°; after recrystallisation from alcohol (yield, 1 g.), the m. p. and mixed m. p. with the compound obtained by method (1) were 113°.

Thiobenz-α-naphthalide (cf. Jacobson, *loc. cit.*).—Benz-α-naphthalide (120 g.) was heated with phosphorus pentasulphide (70 g.); a vigorous effervescence took place. Ethyl alcohol (500 ml.) was immediately added in small amounts because of frothing. The product was heated on a water-bath, made strongly alkaline with sodium hydroxide, diluted with water (1500 ml.), and filtered after 12 hours from a large amount of tar. Acid-free carbon dioxide was passed through the clear solution for 24 hours and the precipitated yellow solid was washed with water and crystallised from alcohol, forming colourless needles (70 g.), m. p. 150°.

2-Phenylnaphtha(1′ : 2′ : 4 : 5)thiazole, prepared from thiobenz-α-naphthalide (70 g.) by Jacobson's method (*loc. cit.*), formed almost colourless needles (35 g.), m. p. 103° to a red liquid (Found: N, 5·2; S, 12·6. Calc. for $C_{17}H_{11}NS$: N, 5·4; S, 12·3%).

2-Phenyl*peri*naphthathiazine, prepared from α-naphthylsulphonyl chloride (Erdmann and Süvern, *Annalen*, 1893, **275**, 230) by Reissert's method (*loc. cit.*), formed yellow-brown needles, m. p. 106° (Found: N, 5·3; S, 12·2. Calc. for $C_{17}H_{11}NS$: N, 5·4; S, 12·3%), mixed m. p. with 2-phenylnaphtha(1′ : 2′ : 4 : 5)thiazole, 80—85°.

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[*Received, December 20th*, 1941.]

NOTES.

The Preparation of 2-Iodobenzoquinone. By HERBERT H. HODGSON and DONALD E. NICHOLSON.

2-Iodobenzoquinone, the remaining unknown monohalogeno-*p*-benzoquinone, has now been prepared by the oxidation of 3-iodo-4-aminophenol with ferric sulphate (cf. Smith and Irwin, *J. Amer. Chem. Soc.*, 1941, **63**, 1036). Ferric chloride and chromic acid, though suitable for the oxidation of the other three 3-halogeno-4-aminophenols, liberated a considerable amount of iodine when reacting with 3-iodo-4-aminophenol, with consequent production of an impure 2-iodobenzoquinone in very inferior yield.

3-Iodo-4-nitrosophenol (3 g.) (Hodgson and Nicholson, J., 1939, 1808) was made into a paste with hydrochloric acid (2 c.c., *d* 1·16) and water (8 c.c.), and the well-stirred mixture reduced near its b. p. by the addition of iron filings (2·5 g.) during 10 minutes. The mixture, after being heated for 5 minutes longer on the water-bath to complete the reduction, was submitted to rapid filtration on a previously warmed Buchner funnel. On cooling, the filtrate deposited 3-iodo-4-aminophenol in colourless plates, m. p. 145° after recrystallisation from boiling water (Hodgson and Kershaw, J., 1928, 2704, give m. p. 144·5°). A further quantity was obtained by three extractions of the residue from the iron reduction with boiling water (10 c.c. each time) (total yield, 1 g.). When the 3-iodo-4-aminophenol (1 g.) was mixed with water (15 c.c.) and ferric sulphate (5 g.) and steam-distilled (the flask could not be externally heated, since iodine then separated), 2-iodobenzoquinone passed over. It crystallised from hot water in orange-red prisms, m. p. 62° (Found: I, 54·1. $C_6H_3O_2I$ requires I, 54·2%), which had a pronounced quinone odour readily distinguished from that of iodine. Oximation was carried out by addition of a slight excess of hydroxylamine hydrochloride, dissolved in the minimum amount of water, to an alcoholic solution of 2-iodobenzoquinone which contained sodium acetate; after 12 hours, the monoxime separated as its stable tautomeride, 2-iodo-4-nitrosophenol; it crystallised from benzene

in yellow needles, m. p. 152° (decomp.) [Hodgson and Moore, J., 1925, **127**, 2260, give m. p. 152° (decomp.)] (Found : N, 5·7; I, 50·9. Calc. : N, 5·6; I, 51·0%).

The authors thank Imperial Chemical Industries (Dyestuffs) Ltd. for gifts of chemicals.—TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, November 11th*, 1941.]

Preparation and Properties of p-*Thiolbenzoic Acid.* By D. BRAMLEY and N. H. CHAMBERLAIN.

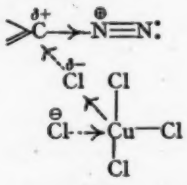
REPETITION of the procedure of Smiles and Harrison (J., 1922, **121**, 2024) for the preparation of this compound gave a white powder containing (by iodine titration) less than 1% of the required thiol. If, however, during reduction of the *p*-chlorosulphonylbenzoic acid, the temperature is maintained at 90—100°, the product is a yellow crystalline powder, m. p. 217°, freely soluble in alcohol, ether and acetone, and containing by iodine titration 99% of thiolbenzoic acid. The specimen contained traces of zinc, which repeated crystallisation from aqueous alcohol failed to remove (Found : C, 53·65; H, 4·0; S, 19·5. Calc. for $C_7H_6O_2S$: C, 54·5; H, 3·9; S, 20·8%).—LEEDS UNIVERSITY. [*Received, February 5th*, 1942.]

An Interpretation of the Sandmeyer Reaction. Part II. Some Corrections. By HERBERT H. HODGSON, STANLEY BIRTWELL, and JOHN WALKER.

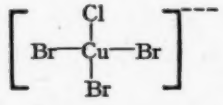
SINCE the publication of Part I (J., 1941, 770), Dr. F. G. Mann has kindly drawn our attention to the fact that there is little reliable evidence for the Cu–Cu link in cuprous compounds as depicted in (I) and (II) of Part I (p. 771), because in those compounds where detailed structure is known, the cuprous atoms are too far apart for such direct linkage; moreover, such structures usually enable the cuprous atoms to acquire 7 electrons and thus attain the krypton structure (cf. Wyckoff and Posnjak, *J. Amer. Chem. Soc.*, 1922, **44**, 30; Davey, *Physical Rev.*, 1922, **19**, 248; Goldschmidt, *Z. Elektrochem.*, 1928, **34**, 459; Mann, Purdie, and Wells, J., 1936, 1503). The active complex cuprous anion in a solution of cuprous chloride in hydrochloric acid will therefore be more correctly represented by (A) than by (I) (*loc. cit.*, p. 771), with the corresponding modification for (II) (*loc. cit.*, p. 771). This formulation would also be in harmony with the established compound, $K_3Cu(CN)_4$, which Grossmann and von der Forst (*Z. anorg. Chem.*, 1905, **43**, 94) have shown represents the most stable type of complex cuprous cyanide.

On analogy for the mixed Sandmeyer reactions, the formulæ for the complex anions of cuprous chloride with hydrobromic acid and of cuprous bromide with hydrochloric acid would then tentatively be (B) and (C), in which the bromine would tend to become δ- rather than the chlorine atoms.

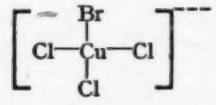
These anionic formulæ would even more readily account for the preponderance of bromo- and chloro-products found respectively when the anions (B) and (C) react with diazonium salts. The proposed mechanism for the reaction is of course undisturbed by this proposal for bringing the structures of the complex anions into line with current data.



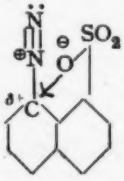
(A.)



(B.)



(C.)



(D.)

Prof. W. M. Cumming also has pointed out to us that the statement concerning the general reaction of iodides with diazonium compounds reported by Saunders ("The Aromatic Diazo-compounds," E. Arnold and Co., London, 1936, p. 154) as found by Cumming and Muir (*J. Roy. Tech. Coll.*, 1936, **3**, 562) requires considerable modification. The actual sentence from Saunders (*op. cit.*) on which we had relied, as the original paper was then not accessible to us, runs as follows : "An exception to this very general reaction has been recently reported by Cumming and Muir, who have found that 1-diazonaphthalene-8-sulphonic acid when treated with potassium iodide in pyridine solution affords *not* the iodo-compound but naphthalene-1 : 8-sultone." It would not be inferred from this statement that the yield of 1 : 8-iodonaphthalene sulphonate had been 70% and that the so-called pyridine solution was composed of 1 c.c. of pyridine in 150 c.c. of water, and the amount of the 1 : 8-naphthasultone, which was not estimated, could not be greater than 30%. Further, when pyridine was absent "the yield of naphthasultone was higher with a corresponding poor yield of iodo-salt, while the formation of 1 : 8-naphthasultone occurred readily when 1-diazonaphthalene-8-sulphonic acid was heated alone or in aqueous solution." This last reaction conforms to the scheme of interpretation given in the Sandmeyer paper, *viz.*, the anionoid sulphuric bound-ion seeks the kationoid carbon to which the diazo-group is attached (D; VII*c*, p. 774 of the first paper).

It would appear, therefore, that in the decomposition of 1-diazonaphthalene-8-sulphonic acid by potassium iodide in the presence of less than 1% of pyridine, two simultaneous reactions occur : (1) the normal decom-

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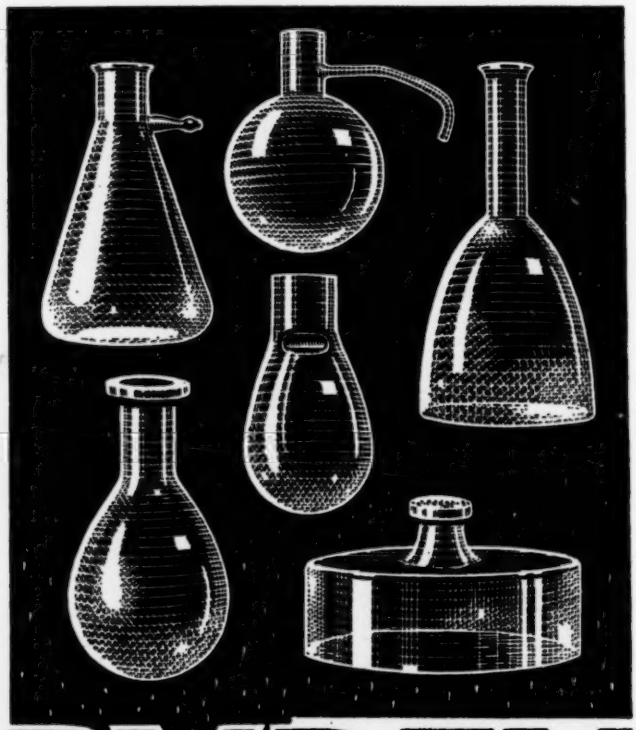

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